

BLOOD FLOW IN HUMAN NASAL MUCOSA

Mats Bende

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From the Department of Oto-Rhino-Laryngology,
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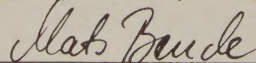
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Abstract The aim of this investigation was to develop a simple method for determining nasal mucosal blood flow in man. Because of the positive experiences of the ^{133}Xe wash-out technique for determination of blood flow in other organs it was selected for use in this study. ^{133}Xe in saline solution was injected into the mucosa of the inferior turbinate. The disappearance of the isotope was followed by a single scintillation detector and the blood flow was calculated from the initial slope of the wash-out curve. With a scintillation camera, the disappearance of ^{133}Xe was studied in detail. In laryngectomees, it was found that most of the isotope disappeared by the blood flow and was eliminated via the lungs to the expired air. Only a negligible part of ^{133}Xe leaked from the mucosa to the nasal air. In healthy subjects the mean nasal mucosal blood flow was estimated to be about $30 \text{ ml} \cdot \text{min}^{-1} \cdot (100\text{g})^{-1}$. With increasing age the blood flow decreased but no difference was obtained between the sexes. A significantly decreased blood flow was found in the sitting position compared to the supine position. In laryngectomees a decreased blood flow in the nasal mucosa was found in comparison to healthy non-laryngectomees. During an acute infectious rhinitis the blood flow increased but in a provoked allergic reaction a decreased nasal mucosal blood flow was obtained. The topical nasal decongestant oxymetazoline significantly decreased the nasal mucosal blood flow in healthy subjects, but another nasal decongestant, phenylephrine, did not change the blood flow. This difference seems to be due to different affinities to α-adrenoceptors on the resistance vessels. The ^{133}Xe wash-out method was found to be applicable to the human nasal mucosa for quantitative evaluation of blood flow in healthy as well as in pathological conditions. The method was also found to be useful when studying effects of vasoactive drugs, important for treatment of nasal disorders.			
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Nog finns det mål och mening i vår färd -
men det är vägen, som är mödan värd.

Karin Boye



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The present thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

- I A method for determination of blood flow with ^{133}Xe in human nasal mucosa.
Accepted for publication in Acta Otolaryngologica.
Together with Knut Flisberg, Ingemar Larsson,
Per Ohlin and Peter Olsson.

- II Blood flow with ^{133}Xe in human nasal mucosa in
relation to age, sex and body position.
Accepted for publication in Acta Otolaryngologica.

- III Blood flow in human nasal mucosa after total
laryngectomy.
Accepted for publication in Acta Otolaryngologica.

- IV The effect of topical decongestant on blood flow
in normal and infected nasal mucosa.
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- V The effect of provoked allergic reaction and
histamine on nasal mucosal blood flow in humans.
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Together with Åke Elner and Per Ohlin.

- VI The role of adrenoceptors in the control of human
nasal mucosal blood flow.
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Together with Karl-Erik Andersson.

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INTRODUCTION

Diseases of the upper respiratory tract, such as common cold and allergic rhinitis, are most frequent and they constitute a considerable medical, social and even economic burden for the individual as well as for society. The respiratory mucosa plays a decisive role in these disorders, but neither the physiology nor the patho-physiology of the mucosa are yet completely understood. Increased knowledge of the physiology and the patho-physiology of the nasal mucosa in man as well as of the effects of various drugs on the complicated vascular structures seems important to improve the treatment of patients with disorders of the respiratory mucosa in general. In the present investigation the nasal mucosal blood flow as well as the effect of different vasoactive substances have been studied during normal and pathological conditions.

Structure and function of the nasal mucosa in man

The morphology of the nasal respiratory mucosa is well known and should only be briefly recapitulated here after Paparella & Shumrick (1980) in order to provide a basis for the understanding of normal nasal function as well as for the present investigation. The anterior part of the nasal chambers, vestibulum nasi, is covered with squamous epithelium. The main part of the human nasal mucosa is lined by a ciliated pseudostratified columnar epithelium except for the olfactory region. The epithelium is covered by a mucous sheet, produced by glands and goblet cells in the mucosa. This mucociliary system is mainly a transport system for particles deposited in the nose, but it has also an important function of defence against microorganisms. Beneath the respiratory epithelium there is a thick lamina propria, "submucosa", which is made up of a loose connective tissue, richly supplied with blood vessels. The blood supply to the nasal mucosa comes from the external carotid artery via the sphenopalatine artery to the turbinates, lateral walls and inferior parts of the septum and from the internal carotid artery via the anterior and posterior ethmoidal arteries to the

superior parts of the nose. The capillary network is well developed in the mucosa. There is also a system of arteriovenous shunts (Sucquet, 1862; Rossatti, 1954) which, when patent, permits a bypass of the capillaries and causes a decreased vascular resistance. The veins of the nasal mucosa form cavernous plexa, the sinusoides, particularly well developed in the middle and inferior turbinates (Cauna, 1982).

The blood flow of the nasal mucosa is controlled by the tone of the resistance vessels, mainly small arteries and arterioles (cf. Mellander & Johansson, 1968). The blood volume in the mucosa, however, is regulated by the capacitance vessels, the venous system including the sinusoids. Variations in smooth muscle tone in the capacitance vessels produce considerable shifts in regional blood content which leads to changes in nasal patency. The condition of the capacitance vessels has been judged by anterior rhinoscopy, rhinomanometry and plethysmography (Ralston & Kerr, 1945; Aschan et al., 1958; Miles Foxen et al., 1971; Broms, 1980). The nasal patency is also to some degree influenced by changes in extracellular fluid, which are dependent on the transudation and the absorption of fluid in the capillaries (Broms et al., 1982), and by changes of the amount of secretion on the mucosal surface. The distribution of blood in parallel capillary systems and arterio-venous shunts in the peripheral circulation is altered continuously by local regulatory mechanisms (Clark & Clark, 1932; 1934; Mellander & Johansson, 1968).

In experimental animals it is found that the nasal blood vessels are extremely sensitive to circulating adrenalin (Malcomson, 1959) but differences in sensitivity to adrenalin and various substances as well as to nerve stimuli are observed between resistance and capacitance vessels (Naumann, 1961; Ånggård & Edwall, 1974; Malm, 1974b; 1974c). Burnham showed as early as 1932 that adrenalin and ephedrine acted in different ways on the human nasal mucosa. After topical application of these drugs the mucosa blanched and decongested. With adrenalin the mucosa blanched rapidly and thereafter followed a decongestion. With ephedrine, on the other hand, the decongestion was primary and

was secondarily followed by a less evident blanching. This reaction demonstrates that the blood volume and the blood flow in the nasal mucosa can act independently of each other (Martin & Friedman, 1973; Proctor & Andersen, 1982).

The nasal mucosa has an important function for respiratory air conditioning but it is probably also engaged in body temperature regulation (cf. Proctor & Andersen, 1982). The mucosa functions as a regenerative heat and moisture exchanger. The inspiratory air is heated and moistened to meet the demands of the respiratory mucosa in the lower airways while the expiratory air transfers some of its heat and moisture back to the respiratory mucosa. The temperature of the respiratory air is mainly regulated by changes in mucosal blood flow, and it is supposed that also the humidification depends on the blood flow (Cauna, 1982). It has been suggested that especially the arterio-venous shunts in the turbinates are responsible for the regulation of respiratory air temperature (Cole, 1982), analogous to the shunt vessels in the skin, which are engaged in thermo-regulation of the body (Clark & Clark, 1934; Mellander & Johansson, 1968).

Methods for measuring nasal mucosal blood flow in man and experimental animals

Several investigations have been performed to evaluate the nasal mucosal blood flow. By direct inspection of the mucosa it is possible to get a rough impression of the blood flow. Increased redness indicates an increased blood flow (Bernheimer, 1934; Drettner, 1961; Jackson & Martinez, 1965). However, the degree of redness only reflects the blood flow in the superficial vessels, but the state of the deeper mucosal vessels cannot possibly be judged by inspection. Another way of studying the superficial blood flow of the nasal mucosa is by means of intravital microscopy (Naumann, 1961). Since the blood flow in superficial and deep blood vessels can vary independently of each other, as is found in different regions of the peripheral circulation (cf. Mellander & Johansson, 1968), the blood flow in the superficial nasal vessels may not be representative for mean

mucosal blood flow in the nose.

Variations in the temperature or thermal conductivity of the nasal mucosa are generally considered to reflect changes in the mucosal blood flow. Numerous and extensive studies have been published on this theme (Mudd et al., 1921; Spiesman, 1936; Ralston & Kerr, 1945; Cole, 1954; Drettner, 1961; Flisberg & Ingelstedt, 1962; Konno & Togawa, 1979). However, the temperature of the nasal mucosa is influenced by other factors than the blood flow, such as changes in environment temperature and in blood content (Biesalski & Marquardt, 1959; Drettner, 1961). Furthermore the relationship between blood flow and temperature is probably not linear (Drettner, 1961; Golenhofen et al., 1963), which restricts its scientific application. The thermo-technical methods have mainly been used to study the nasal vascular reactions on exposure to cold and not for evaluating the effect of vasoactive drugs on the nasal mucosa. To conclude, all these indirect methods give only a rough estimate of the nasal blood flow.

Konno et al. (1982) have described a method for evaluating nasal mucosal blood flow in subjects with nasal allergy. The method is a modification of the hydrogen clearance method, presented by Aukland et al. (1964). The subject is saturated with a hydrogen-air mixture. With an electrode located in the nasal mucosa, the disappearance of hydrogen is followed, and the blood flow is calculated from the slope of the wash-out curve. The significance of this method is not yet fully evaluated.

Various quantitative methods have also been used to study nasal mucosal blood flow in experimental animals. Thus, radioactive-labelled microspheres (Abe & Jackson, 1972; Clairmont et al., 1973; Ånggård, 1974b) or ^{125}I -iodide (Ånggård & Edwall, 1974) have been injected into the arterial system or applied locally and the appearance or disappearance of the tracer was measured by means of scintillation detectors to evaluate blood flow. The most direct way of determining nasal mucosal blood flow is to measure the venous outflow from the mucosa (Malm, 1974a). However, these quantitative methods can not be used in humans and

it is difficult to extend reliable conclusions about drug effects from experimental animals to humans.

Thus, to conclude, previous investigations could not quite satisfy the need for a simple method for quantitative calculations of the nasal mucosal blood flow in humans. The positive experiences of the ^{133}Xe wash-out technique for determination of blood flow in various organs created opportunities for evaluation of the merits of this method in nasal mucosal blood flow analysis.

PURPOSE OF THE STUDY

Although nasal mucosal blood flow is of major importance for the function of the mucosa in healthy as well as in pathological conditions, it has not been studied extensively in man, since a simple, reproducible method for estimation of mucosal blood flow is lacking. Symptomatic nasal drugs, like topical decongestants, antihistamines and corticosteroids are widely used. The clinical effects of these drugs are well known, but the mode of action is still poorly understood. From both a physiological and a clinical point of view, the effect on the nasal mucosal blood flow of substances used in nasal disorders would be of interest to study.

The present investigation was therefore performed:

1. to develop a simple method for determining nasal mucosal blood flow (I, II)
2. to investigate possible differences in nasal mucosal blood flow according to sex, age and body position (II)
3. to evaluate the effect on mucosal blood flow of acute infectious and in provoked allergic reactions (IV, V)
4. to study the mucosal blood flow after total laryngectomy (III)
5. to investigate the effect of different vasoactive substances especially nasal decongestants (IV, V, VI)
6. to identify the adrenoceptors of importance for the nasal mucosal blood flow (VI).

THE PRESENT INVESTIGATION

The ^{133}Xe wash-out method for determination of human nasal mucosal blood flow (I and II)

Radioactive wash-out techniques have been used frequently to determine organ blood flow since the introduction of the method by Kety (1949; 1951). The proposal to use the inert radioactive gas ^{133}Xe for muscle blood flow (Lassen et al., 1964; Holzman et al., 1964) has been followed by several investigations using the ^{133}Xe wash-out technique in man and experimental animals on muscle, kidney, skin, intestine, myocardium, bone, uterus and brain (e.g. Höedt-Rasmussen et al., 1966; Ladefoged, 1966; Sejrsen, 1967; Tønnesen, 1969; Wilson et al., 1975; Haunsö et al., 1979; Lahtinen et al., 1979; Daly & Henry, 1980; Ottesen, 1980; van Duyl & Volkers, 1980). It therefore seemed natural to study the value of this well established technique for evaluation of the blood flow in the nasal mucosa in man.

Procedure. 0.1 ml of ^{133}Xe , containing 1-10 MBq, in an isotonic NaCl solution was injected into the mucosa of the inferior turbinate. The disappearance of the isotope was followed by a single scintillation detector. A scintillation camera was used to follow the leakage of ^{133}Xe from the mucosa to the nasal air and spreading of the tracer in the mucosa from the site of injection, as well as the activity in the expired air collected from the tracheostoma in laryngectomees. The nasal air was sucked by a pump through a carbon trap to collect the ^{133}Xe that leaked from the mucosa to the nasal air. With the scintillation camera over the subject's face and the carbon trap, it was possible to study the leakage of the isotope. The expired air from the tracheostoma was collected in a gas tight bag and the activity was recorded. The blood flow was calculated from the initial slope of the disappearance of the isotope (Lassen, 1967), using a formula presented by Lassen et al. (1964):

$$f = \frac{\ln 2 \cdot \lambda \cdot 100 \cdot 60}{T_{\frac{1}{2}}}$$

where λ represents the partition coefficient at equilibrium for ^{133}Xe between tissue and blood, i.e. the ratio between the concentration of the tracer in the tissue and in the blood. As the fat content in the nasal mucosa is low (1), a standardized value of $0.7 \text{ ml} \cdot \text{g}^{-1}$ was used for λ , in accordance with previous recommendations for tissues with low fat content (Lassen et al., 1964; Ladefoged, 1966; Sejrsen, 1971).

In order to evaluate the usefulness of the ^{133}Xe wash-out method and to standardize the technique, the following factors were analyzed:

1. The disappearance of ^{133}Xe from the mucosa by blood flow.
2. The disappearance of ^{133}Xe by leakage from the mucosa to the nasal air.
3. The spreading of ^{133}Xe in the nasal mucosa from the site of injection.
4. The nasal mucosal blood flow in a material of healthy subjects.
5. The reproducibility of the method.
6. The influence of sex differences on blood flow.
7. The influence of age on blood flow.
8. The effect of body position on blood flow.
9. The effect of mouth- and nose-breathing on blood flow.

Results. ^{133}Xe in the venous system was efficiently eliminated in the lungs. Since about 95 % of the ^{133}Xe from the nasal mucosa, was found in the expired air, it is stated that the injected ^{133}Xe disappeared mainly by the blood flow. The initial slope of the ^{133}Xe wash-out curve was shown to be valid for

calculation of the nasal mucosal blood flow in humans. Only a small amount, about 5%, leaked from the mucosa to the nasal air. The spreading of ^{133}Xe in the mucosa was limited to a rather small area.

The blood flow at rest in a reference material of healthy subjects ($n = 80$) was $33 \pm 10 \text{ ml} \cdot \text{min}^{-1} (100 \text{ g})^{-1}$ (mean $\pm$ SD). From duplicate determinations, the coefficient of variation was calculated to 22 %, but the difference of means between the duplicate determinations on a group of subjects was small. No sex-related differences were found, but blood flow decreased with increasing age. A significantly decreased blood flow was found in the sitting position compared to the supine position. No differences in blood flow were seen between nose- and mouth-breathing.

Conclusion. A well standardized ^{133}Xe wash-out method seems to be valuable for studies of blood flow changes in the human nasal mucosa.

Effects on nasal mucosal blood flow of vasoactive drugs (IV, V, and VI)

Nasal decongestants, such as oxymetazoline and phenylephrine, are frequently used in disorders of the upper respiratory tract. They have a well-documented vasoconstricting effect on the capacitance vessels resulting in a decrease in mucosal thickness and thereby an increased nasal patency (cf. Gilman et al., 1980). However, the effect of nasal decongestants on the resistance vessels and thereby on the blood flow has not been completely evaluated. Such an evaluation would be of primary interest for understanding the mode of action of the substances as well as of the adverse effects of the drugs. The purpose of these investigations was to study the effects of nasal decongestants and other vasoactive substances on nasal mucosal blood flow, and to identify the adrenoceptors of importance for the blood flow.

Procedure. The effect of oxymetazoline (α -adrenoceptor agonist) on nasal mucosal blood flow was investigated in 18 healthy subjects and in 8 subjects with acute infectious rhinitis. Oxymetazoline was given topically in therapeutically recommended doses, three drops containing about 0.05 mg, the most common way of applying nasal decongestants. In additional experiments, the effect of various doses of oxymetazoline, from 0.001 to 0.3 mg, was evaluated in 5 healthy subjects.

For comparison, the effect of phenylephrine on mucosal blood flow was evaluated in 6 healthy subjects. Phenylephrine was applied in the same way as oxymetazoline and in an equivalent dose (0.25 mg). Oxymetazoline and phenylephrine are both α -adrenoceptor agonists, but oxymetazoline acts preferentially on α_2 -adrenoceptors and phenylephrine on α_1 -adrenoceptors (cf. Starke, 1981). To verify the importance of the α_2 -adrenoceptors for the blood flow, further experiments were performed on healthy subjects with an α_2 -adrenoceptor agonist, clonidine, and a selective α_2 -adrenoceptor antagonist, yohimbine. The doses of clonidine, about 50 μ g, and yohimbine, 0.2 mg applied topically, were chosen after pilot experiments.

To evaluate the effects on blood flow of β_2 -adrenoceptors, a selective β_2 -adrenoceptor agonist, terbutaline (2.5 mg), was tested alone and in combination with oxymetazoline in 13 healthy subjects. Topical application was chosen to secure a high local concentration of the substance.

The effect on blood flow of locally injected histamine, an effective vasodilator, was evaluated in 10 healthy subjects and in 10 subjects with allergic rhinitis in a dose of about 20 μ g.

Results. Clinical doses of oxymetazoline decreased the nasal mucosal blood flow by about 50%. In subjects with acute infectious rhinitis, the effect was relatively more marked than in healthy subjects. Oxymetazoline (α_2 -adrenoceptor agonist) significantly decreased the mucosal blood flow in doses from 0.001 mg in a dose-dependent way. The α_2 -adrenoceptor agonist clonidine also decreased the blood flow. With the α_2 -antagonist yohimbine, the effect of oxymetazoline and clonidine was inhibited, but yohimbine did not per se increase the blood flow. Phenylephrine (α_1 -adrenoceptor agonist) did not change the blood flow significantly in therapeutically recommended doses. Terbutaline (β_2 -adrenoceptor agonist) was used in a high dose, which sometimes caused systemic effects. In spite of that, no effects were observed on normal blood flow or on the oxymetazoline decreased blood flow. Histamine was found to increase the blood flow significantly in healthy subjects as well as in symptom-free subjects with allergic rhinitis.

Conclusion. The ^{133}Xe wash-out method was found to be useful for evaluating the effects of the vasoactive drugs, e.g. nasal decongestants, on blood flow in the human nasal mucosa. The results suggest that the blood flow in the human nasal mucosa is mainly controlled via α_2 -adrenoceptors while α_1 - and β_2 -adrenoceptors are probably of minor importance.

Nasal mucosal blood flow in acute rhinitis, in provoked allergic reaction, and in laryngectomees (III, IV, and V)

The nasal patho-physiology in such disorders as viral and bacterial infection and allergy as well as after laryngectomy is only partly clarified. In laryngectomees morphological changes in the mucosal vascular bed have been described but no blood flow studies have been performed. Studies of the nasal blood flow in these pathological conditions are therefore of great interest. Thus, in the present investigation the nasal mucosal blood flow was studied in acute infectious rhinitis, after allergic provocation and after total laryngectomy.

Procedure. Eight subjects were investigated during an early stage of acute infectious rhinitis and in healthy condition. Ten other subjects with a known allergic rhinitis were studied before and after allergen provocation. In addition the nasal mucosal blood flow was investigated in 10 subjects who had been submitted to total laryngectomy. The blood flow in the allergic subjects and in the laryngectomees was compared with that of healthy subjects (II and III).

Results. A significant increase of mucosal blood flow was found during acute infectious rhinitis. During a provoked allergic reaction, however, the blood flow decreased significantly. The blood flow in subjects with allergic rhinitis without symptoms did not differ significantly from that in healthy subjects. It was found that laryngectomees had a significantly decreased mucosal blood flow compared to healthy subjects.

Conclusion. The ^{133}Xe wash-out method showed notable differences of nasal mucosal blood flow in disease. Thus, an important difference was found between acute infectious rhinitis and a provoked allergic reaction. The decreased blood flow after laryngectomy might confirm in a functional way the morphological changes in the mucosal vessels found in earlier investigations.

GENERAL DISCUSSION

Methodological considerations

The radioactive inert gas ^{133}Xe has certain qualities which make it suitable for studies of blood flow in various tissues. The emitted gamma-radiation is easily detected with scintillation detectors. An inert gas is defined as follows: it dissolves in the blood and the tissue in a manner that can be described by Henry's Law, it suffers no change in chemical identity during its passage through the organism, and it is therefore quantitatively recoverable from the organism at any time (Kety, 1951). ^{133}Xe is considered to be freely diffusible in the tissue and the blood-tissue diffusion equilibrium is therefore efficient and rapid even at high blood flow rates (Lassen et al., 1965; Tønnesen & Sejrsen, 1967; Sejrsen & Tønnesen, 1968); this is a prerequisite for quantitative blood flow determinations (Kety, 1951). During one single lung passage, ^{133}Xe is rapidly eliminated from the blood to the expired air, and therefore recirculation is negligible for calculations of blood flow (Lassen et al., 1964; Ladefoged, 1966). This property gives ^{133}Xe the advantage of having a very short biological half-time in tissues with high blood flow rate, although its physical half-time is 5.3 days. For reasons mentioned above, the ^{133}Xe wash-out method is well suited for blood flow determination in the human nasal mucosa.

The elimination of ^{133}Xe from the nasal mucosa is mainly dependent on blood flow but there are other routes by which the tracer may leave the tissue. Diffusion out from the mucosa to the air in the nasal cavity, indicated in experiments on corpses (I), is probably the second main pathway. This was analyzed on laryngectomees (I) and found to be of minor importance. Other possible ways of disappearance are by the lymph flow and by diffusion to underlying bone. It has not been possible to evaluate these pathways, but one can assume that they are negligible in the calculations of the nasal mucosal blood flow in man.

It should be emphasized that the blood flow rate varies in different blood vessels and that an uneven flow distribution between "parallel-coupled" vascular circuits is common (Mellander & Johansson, 1968). It is therefore likely that the rate of nasal mucosal blood flow varies in different blood vessels. For that reason the best way to express the nasal blood flow is as the mean mucosal blood flow (cf. Wilson et al., 1975), which can be calculated from the initial slope of the wash-out curve. This is done under the presumption that a very rapid diffusion equilibrium is obtained between the mucosa and blood during the passage of the blood through the tissue and that the partition coefficient between the tissue and the blood, λ , is constant. It is assumed that these prerequisites are valid, not from our own studies, but according to investigations performed mainly on muscle and skin (Lassen et al., 1964; Sejrsen, 1967; Tønnesen, 1969).

The injection procedure may alter the nasal mucosal blood flow. The injection trauma increases the blood flow in tissues with low perfusion rate (Sejrsen, 1968), but it is probably of less importance in tissues with more rapid blood flow (Lassen et al., 1965). The effect of the injection trauma might be reduced by using a careful technique and by waiting an appropriate time before starting the measurement (I). Since the ^{133}Xe wash-out is considered to express the mean blood flow of the mucosa, damage to isolated vessels may have little influence on the recordings. The insignificant difference of means from duplicate determinations in the same subjects support the assumption that the influence of the injection trauma is about the same in each examination. The reproducibility of the method, expressed as the coefficient of variation, is 22%. The magnitude of the coefficient of variation can be explained by other methodological factors than the injection trauma as well as by actual variations in blood flow.

The reference values of mucosal blood flow of the upper respiratory tract have been gathered from the literature. The nasal mucosal blood flow in man was found to be about 80 (Konno et al., 1982) and $115 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (Tanimoto et al., 1982)

with the hydrogen clearance method. With a ^{133}Xe gas absorption method the mean mucosal blood flow of the maxillary sinus has been determined as 125 (Drettner & Aust, 1975) and $80 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (Aust et al., 1978). The discrepancies of mean blood flow between different studies (including the present one) are probably related to the individual characteristics of the methods. The higher blood flow values of the hydrogen clearance method may be explained by the more continuous trauma in the mucosa (V). The ^{133}Xe gas absorption method takes into consideration the thickness of the mucosa when calculating the blood flow. After supplementary data on mucosal thickness, the blood flow of the sinus mucosa will be $30\text{--}40 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (Drettner, 1982). Thus, the mean nasal mucosal blood flow in healthy subjects in the present investigation ($33 \pm 10 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$) is in accordance with the values from the sinus mucosa. It should be stressed, that the absolute value of the blood flow may not coincide exactly with the blood flow calculated from the disappearance of ^{133}Xe . However, the ^{133}Xe wash-out method is very suitable for measuring the nasal mucosal blood flow and seems to be the most reliable to date.

Pharmacological considerations

Many patients administer nasal decongestants too frequently and for too long a time, due to the remarkable effect of topical nasal decongestants on mucosal swelling. Nasal decongestants have the disadvantage that continued and intense use may be followed by a "rebound" phenomenon, characterized by a reactive congestion and tachyphylaxia, which requires increased and more frequent doses. This "rebound" phenomenon persists for as long as the patient continues to use the vasoconstrictor (Proctor & Adams, 1976; Gilman et al. 1980). The specific process involved in the development of the "rebound" congestion has not been clarified, but one suggestion is that it is due to a tissue hypoxia (Kully, 1945; Hall & Jackson, 1968; Eccles, 1982). Therefore, an evaluation of nasal mucosal blood flow after application of nasal decongestants seems to be extremely important. The ^{133}Xe wash-out method offers a possibility to analyse this theory and, combined with other methods (e.g. rhinomanometry), the "rebound" phenomenon after long-term use of topical decongestants.

Nasal decongestants can be divided into two groups: sympathomimetic amines and imidazoline derivatives, which both act as vasoconstrictors by influencing the α -adrenoceptors on vascular smooth muscle (Gilman et al., 1980). While sympathomimetic amine derivatives (e.g. phenylephrine) act preferentially on α_1 -adrenoceptors, imidazoline derivatives (e.g. oxymetazoline) act more selectively on α_2 -adrenoceptors (cf. Starke, 1981). Both α_1 - and α_2 -adrenoceptors seem to exist on the capacitance vessels, since both types of substances are effective as nasal decongestants.

The findings in this investigation (VI) that α_2 -adrenoceptors are important for the regulation of the resistance vessels in the human nasal mucosa, give further information about the nasal vascular regulation, which might be clinically essential. The decreased blood flow after nasal decongestants, such as the α_2 -adrenoceptor agonist oxymetazoline, might be harmful to the nasal mucosa (Kully, 1945; Drettner, 1961; Ånggård, 1974a; Black

& Remsen, 1980). Therefore, with a similar decongestive effect, a nasal decongestant having a selective α_1 -adrenoceptor stimulating effect seems preferable to a drug mainly acting on α_2 -adrenoceptors. As a statistically significant reduction of blood flow was found in doses as low as 1/50 of the approximate therapeutically recommended dose with commercially available oxymetazoline (IV), it might be possible to attain a clinically sufficient nasal patency by lower doses of oxymetazoline than we use today. However, comparative studies of the decongestive beneficial effect of nasal decongestants are contradictory and not conclusive, and further investigations are desirable.

The existence of β -adrenoceptors in the nasal mucosal vessels has been investigated in several studies, but the results are contradictory (cf. VI). Most vascular beds contain both contraction-mediating α -adrenoceptors and relaxation-mediating β -adrenoceptors (McGrath, 1981). The β_2 -adrenoceptor agonist terbutaline was used in this study to identify β -adrenoceptors in the resistance vessels. Since no effect on nasal blood flow was obtained using terbutaline in sufficient doses, it is suggested that β_2 -adrenoceptors are of minor importance for blood flow regulation.

The effect of histamine on nasal mucosal blood flow is of great interest, since histamine is one of the primary mediators in the allergic reaction. Histamine increased nasal blood flow due to dilation of the resistance vessels both in healthy and in allergic subjects (V). An increased mucosal thickness, indicating also a dilation of the capacitance vessels has been demonstrated both in humans and in experimental animals after histamine administration (Bentley & Jackson, 1970; Hiley et al., 1978; Cole et al, 1980). However, the vasodilatory effect of histamine probably depends on the administered dose and it is possible, that even a vasoconstriction can be obtained with increased doses, as shown in rabbits (Naumann, 1961). In this study, the dose was chosen to give vasodilation (Sejrsen, 1967), in order to confirm that the ^{133}Xe wash-out method was suitable also for registrations of an increased blood flow (I).

Clinical considerations

The acute inflammatory reaction is generally characterized by an increase in blood flow and vascular permeability and migration of leukocytes. The increased blood flow (IV) and an increased temperature (Biesalski & Marquardt, 1959; Drettner, 1961) observed in the human nasal mucosa during an acute rhinitis are attributed to the inflammatory reaction. The question is whether the increased blood flow is a by-product of the pathological process or a basic defence mechanism of benefit to the patient. There has recently been a similar discussion about fever, as a response to infection. Thus, it is proposed that the elevation in body temperature during disease is a response of the body to infection rather than a passive by-product of disease and considerable evidence has accumulated that moderate elevation of body temperature is beneficial to an infected host (cf. Roberts, 1979; Kluger, 1980). Analogously to this discussion, the increased blood flow in the nasal mucosa during an infection would also be beneficial. Some hesitation has therefore been expressed for using topical decongestants with vasoconstrictor effect on the resistance vessels in infectious rhinitis (Butler & Ivy, 1944; Kully, 1945; Drettner, 1961; Ånggård, 1974a; Malm, 1977), but whether they delay the healing process has not been evaluated. A comparative study in this respect between nasal decongestants with and without influence on the resistance vessels would therefore be of particular interest.

The mucosal blood flow decreased in subjects with allergic rhinitis after allergen provocation. This was a surprising finding in view of the release of vasodilating mediators, among them histamine, in allergic reactions and indicates a complicated interplay between different mediators on the vascular bed. In studies of drug effects on allergic rhinitis, allergen- and histamine-induced nasal congestions have been used as experimental models (Slome, 1956; Bentley & Jackson, 1970; Salem & Clemente, 1972; Pelikan & de Vries, 1974; Svensson et al., 1981; Pipkorn, 1982). No attention is paid to the nasal blood flow. The reverse effect on blood flow of histamine and of the pro-

voked allergic reaction in this study (V) might suggest that these experimental models could be questioned, when only one function is analysed. For reliable results, more comprehensive examinations should be of interest in the future.

The existence of morphological changes in the nasal mucosa after total laryngectomy or permanent tracheostomy has been discussed. Some authors (Sternberg, 1924; Topozada & Gaafar, 1976) found microscopic changes in the mucosa indicating a decreased blood flow, while others did not (Dixon et al., 1949; Schwab, 1955). Functionally, it has been found that the nasal cycle disappears after laryngectomy (Keuning, 1968). This seems to be due to effects on the capacitance vessels. The present investigation (III) showed that the nasal mucosal blood flow decreased after laryngectomy. This finding suggests an effect also on the resistance vessels, which could be a contributory cause for morphological and functional changes after laryngectomy. The mechanism behind the effects on the nasal mucosal blood vessels after laryngectomy is not clear. The abolished air current through the nose may be the reason of the changes in the nasal mucosal vessels. This may be a direct effect, e.g. reduced stimulation, on the nasal mucosa. On the other hand it might also be an indirect effect. Experimental studies suggest that there is a relationship between the upper and lower respiratory airways based upon different reflex mechanisms (cf. Cole, 1982).

GENERAL SUMMARY

A method for determining the blood flow in human nasal mucosa based on the wash-out of locally injected ^{133}Xe is presented.

Various factors, which may influence the results, e.g. disappearance of ^{133}Xe by other routes than by blood flow, influence of body position, age and sex are analysed. The ^{133}Xe wash-out method permits an easy detection of blood flow changes in the nasal mucosa and gives reproducible results. Furthermore, with the ^{133}Xe wash-out method determination of blood flow in health and during disease can be evaluated, as well as effects of various vasoactive drugs.

The nasal decongestant oxymetazoline induced a dose-dependent decrease of nasal mucosal blood flow in healthy subjects. In subjects with an acute infectious rhinitis an increased blood flow was found and the effect of oxymetazoline was more pronounced than in healthy subjects. However, another common nasal decongestant, phenylephrine, did not change the blood flow significantly. The clinical importance of these findings is discussed in relation to the specificity to α -adrenoceptors of these drugs. β_2 -adrenoceptors seem to be of minor functional importance for the blood flow in the human nasal mucosa.

After provocation with pollen, subjects with allergic rhinitis obtained a decreased blood flow in the nasal mucosa. This finding is discussed against the background that histamine increased the blood flow.

In laryngectomees, a decreased blood flow was found compared to healthy subjects.

Conclusion. The ^{133}Xe wash-out method is found to be suitable for quantitative evaluation of blood flow in the human nasal mucosa. The knowledge of the blood flow in the human nasal mucosa in health and disease and the effect on blood flow of various drugs, seems important in the treatment of patients with

nasal disorders and indicates possibilities for a more selective choice of drugs for nasal diseases.

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A METHOD FOR DETERMINATION OF BLOOD FLOW WITH ^{133}Xe IN HUMAN NASAL MUCOSA

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Abstract. The ^{133}Xe wash-out technique was used as a method for calculation of the blood flow in human nasal mucosa. The disappearance of ^{133}Xe from the nasal mucosa was followed using scintillation detectors. In laryngectomees it was shown that the disappearance of ^{133}Xe from the mucosa depended mainly on the blood flow. Leakage of ^{133}Xe from the mucosa to the nasal air was unimportant. The disappearance rate of ^{133}Xe was decreased by oxymetazoline and increased by histamine, most likely due to the effects of these vasoactive drugs on the mucosal blood flow. The ^{133}Xe wash-out technique would seem to be a simple method to study nasal mucosal blood-flow changes in humans.

Various methods have been used for experimental studies on vascular reactions in the nasal mucosa. There have been three main approaches, viz. indirect studies on blood content, and indirect or direct methods of blood-flow determination. The direct methods have been used only on experimental animals (Abe & Jackson, 1972; Änggård, 1974; Änggård & Edwall, 1974; Malm, 1974).

In man, changes in the blood content of the nasal mucosa have been studied indirectly with different techniques, including rhinomanometry (Miles Foxen et al., 1971; Broms, 1980) and plethysmography (Ralston & Kerr, 1945), and the nasal blood flow has been estimated indirectly by measuring changes in temperature or thermal conductivity in the mucosa (Ralston & Kerr, 1945; Drettner, 1961). Photometrically determined colour changes of the nasal mucosa have also been used to indicate changes in blood flow (Jackson & Martinez, 1965).

A direct method to determine the nasal mucosal blood flow in humans has not yet been devised. As has been stressed by several authors (Brain, 1969; Abe & Jackson, 1972; Andersson et al., 1976) there is a need for a simple, useful, direct method. The isotope wash-out technique (Kety, 1949), developed for ^{133}Xe and modified by Lassen et al. (1964), has been widely used both in experimental and clinical studies on regional blood flow in skin, intestine, myocardium, myometrium and cerebrum (Sejrsen, 1971; Wilson et al., 1975; Haunsø et al., 1979; Ottesen, 1980; Marcus et al., 1981).

The present investigation was performed to evaluate the ^{133}Xe wash-out technique as a means for measuring the nasal mucosal blood flow. For this purpose the disappearance of ^{133}Xe was followed in a small reference group before and after application of vasoactive drugs, in laryngectomees and in corpses.

MATERIAL AND METHODS

The experiments were performed on healthy men and laryngectomees. 0.1 ml of ^{133}Xe , 1–10 MBq, in an isotonic NaCl solution was injected into the mucosa in the anterior and medial part of the right inferior turbinate through a 0.4 mm (outer diameter) needle. The injection was made during 15 sec and the needle was not removed until after another 15 sec to prevent reflux. The disappearance of ^{133}Xe was followed using a single scintillation detector or



Fig. 1. Experimental arrangement for determination of disappearance of ^{133}Xe from the nasal mucosa with a single scintillation detector and a scaler-timer.

a scintillation camera as described below. All subjects were examined in the supine position after at least 2 min rest. The head was slightly elevated so that the tip of the nose was standardized to be about 20 cm above the heart level (Fig. 1). The head was fixed with sandbags or a forehead strip. The non-laryngectomies were breathing through the nose. Room temperature was kept at 21–22°C. The absorbed radiation dose was calculated to 1–30 $\text{mGy} \cdot \text{MBq}^{-1}$ locally in the nose and less than $0.2 \mu\text{Gy} \cdot \text{MBq}^{-1}$ as the gonade dose.

1. Disappearance of ^{133}Xe Studied by a Single Scintillation Detector

A. scintillation NaI(Tl)-detector (diameter 50×10 mm) with a collimator (diameter and depth 50 mm) connected to a scaler-timer was

used for the measurements (Trombograph-11, Meditronic, Sweden). The detector was placed as close as possible over the nose (Fig. 1). The number of counts was determined over a 10-sec period every 30 sec. All values were corrected for background. The wash-out curves (counting rate versus time) were then plotted on a semilogarithmic paper.

In 3 healthy men (age 31, 33 and 50 years) three determinations lasting 45 min were performed. These three determinations were used as 'reference curves' (see Fig. 2) for the wash-out of ^{133}Xe . The same 3 men were used for studies with vasoactive substances (see below).

Studies with vasoactive substances

In order to influence the blood flow of the nasal mucosa, oxymetazoline chloride (Nezer-

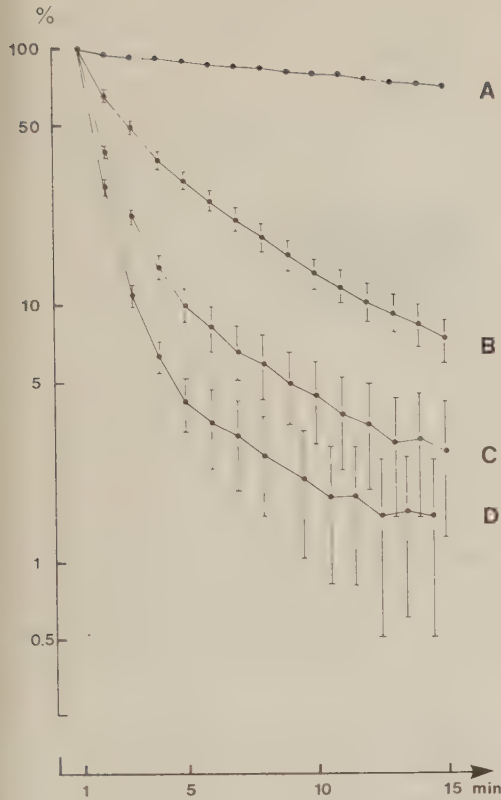


Fig. 2. ^{133}Xe wash-out curves from human nasal mucosa in two corpses (coincident) (A), three recordings after oxymetazoline chloride administration (B), three recordings without drug influence (C), and three recordings after histamine dihydrochloride administration (D). The curves B-D were achieved from three healthy men. All figures (mean $\pm$ SEM) are given as percentages with the first recorded value set to 100%.

il®, Draco, Sweden) and histamine dihydrochloride were used in additional experiments. In three determinations, 1 ml oxymetazoline chloride ($0.5 \text{ mg} \cdot \text{ml}^{-1}$) was dropped onto the inferior turbinate 15 min before injection of ^{133}Xe . In three other determinations, 0.1 ml histamine dihydrochloride ($1 \text{ mg} \cdot \text{ml}^{-1}$) was added to 0.4 ml ^{133}Xe solution and 0.1 ml of the mixture was injected into the mucosa as described above.

Recordings in corpses

Recordings of the ^{133}Xe disappearance after injection in the right inferior turbinate were also made in two corpses.

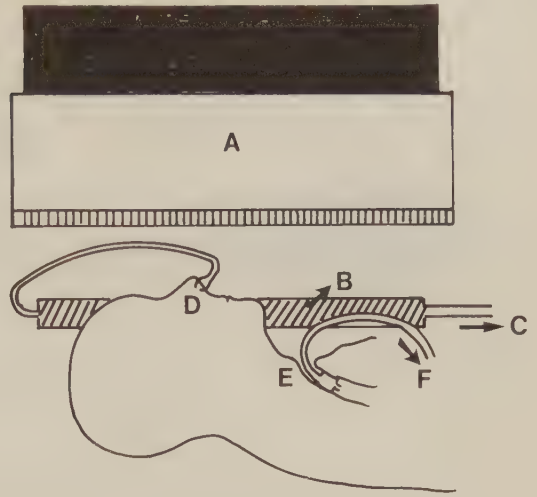


Fig. 3. Schematic drawing of the experimental set-up for estimating ways of disappearance of ^{133}Xe injected into the nasal mucosa in laryngectomees. A = detector head of a scintillation camera; B = carbon-trap; C = to air pump; D = nostril air collector; E = cuffed tracheostomy tube; F = to metallic bag.

II. Disappearance of ^{133}Xe Studied with a Scintillation Camera

The disappearance of ^{133}Xe from the nasal mucosa was studied in detail using a scintillation-camera technique. A scintillation camera (Searle-LFOV) with a low energy parallelhole collimator or a pinhole collimator was used. A microprocessor-based digital system (Searle-Scintiview) was connected to the scintillation camera. The distribution of ^{133}Xe could be displayed and regions of interest drawn with a light pen to generate time-activity curves. Images and curves showed continuously the course of events regarding the disappearance of ^{133}Xe .

Disappearance by blood flow

These determinations were performed in 2 laryngectomees (age 67 and 75 years). ^{133}Xe was injected into the nasal mucosa as previously described. ^{133}Xe eliminated by the

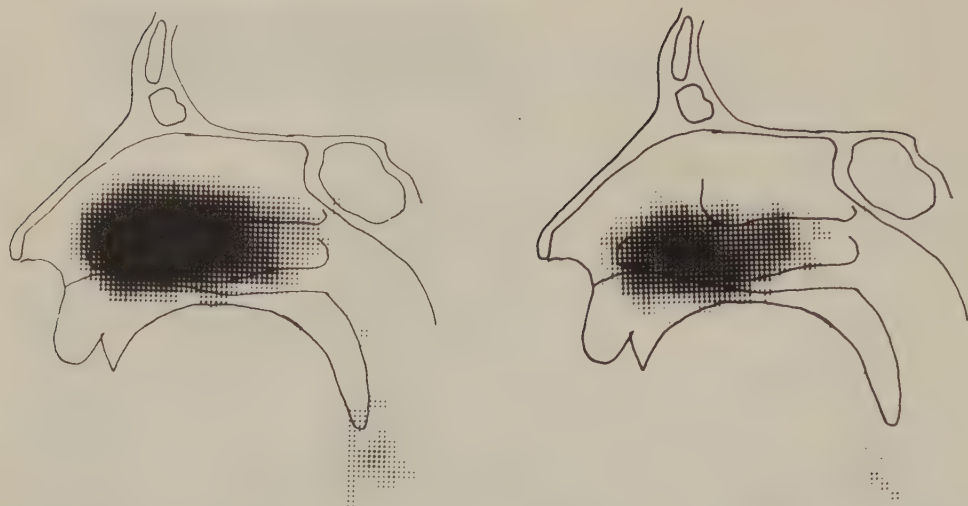


Fig. 4. Two sequential lateral images, taken by a scintillation camera 1-3 (left) and 3-5 (right) min after the injection of ^{133}Xe into the mucosa of the inferior turbinate. The

anatomical structures of the nose are drawn schematically.

blood flow should be found in the expired air. Therefore, all expired air from the tracheostoma, the airway being 'sealed' with a cuffed tube, was collected from 1-5 min after the injection into a metallic bag impermeable for xenon gas (Fig. 3). To calculate the part of ^{133}Xe expired during an experiment the counting-rate from the bag was compared with that from a bag with a known activity of ^{133}Xe . The scintillation camera without collimator was used for these determinations of ^{133}Xe in the bag.

Time-activity curves were generated from regions of interest limited to the site of injection. These curves, representing the total ^{133}Xe disappearance, were analysed from 1-5 min after injection. In this way it was possible to estimate the activity in the mucosa after 1 and 5 min, respectively. By comparing these activities with the activity of ^{133}Xe in the expired air, the part of ^{133}Xe eliminated by the blood flow could be calculated. The wash-out curves could also be used for calculation of the mucosal blood flow (see below). In the laryngectomees the ^{133}Xe wash-out curves

were also determined by the single scintillation detector.

Disappearance by leakage from the mucosa to the nasal air

The air from the actual side of the nose in one of the laryngectomees (age 67 years) was sucked by a pump (capacity $17 \text{ l} \cdot \text{min}^{-1}$). The air was passed through a deep-frozen carbon trap placed in the camera field of view together with the patient's face (Fig. 3). When air passed through the carbon-trap, the ^{133}Xe was absorbed (Bolmsjö & Persson, 1982). It was then possible to generate time-activity curves for estimation of leakage of ^{133}Xe .

Spreading of ^{133}Xe in the inferior turbinate

In 3 healthy subjects (age 28, 29 and 34 years) lateral views of the head were taken to visualize the spreading of ^{133}Xe in the nasal mucosa from the site of injection. For orientation, the anterior and posterior ends of the inferior turbinate were marked by a point source ($[^{99}\text{Tc}^{\text{m}}]\text{pertechnetate}$).

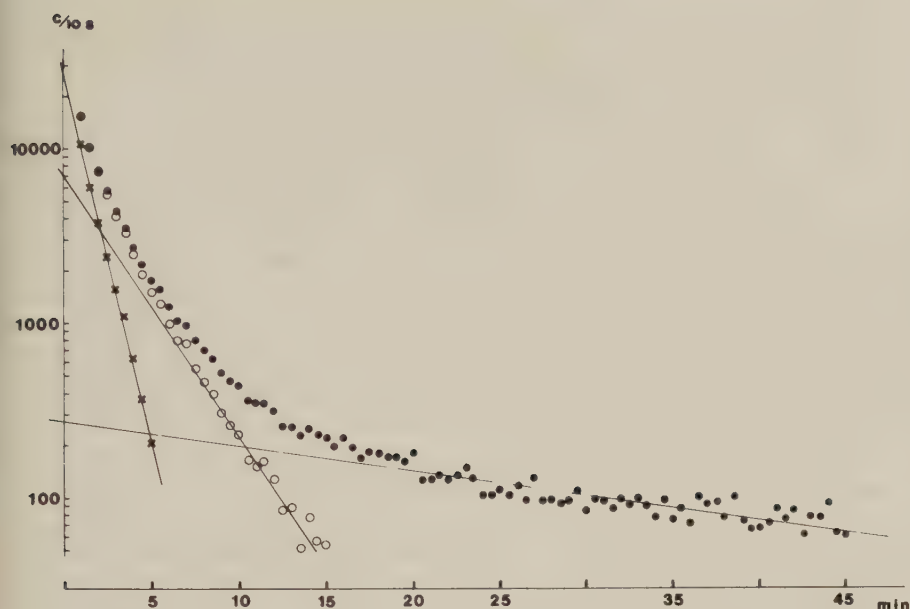


Fig. 5. A ^{133}Xe wash-out curve (●) after injection of ^{133}Xe into the nasal mucosa. Three monoexponential compo-

nents can be distinguished: $\times$ — $\times$, first component; $\bigcirc$ — $\bigcirc$, second component; —, third component.

III. Blood Flow Calculation

The mucosal blood flow (f) was calculated using a formula presented by Lassen et al. (1964):

$$f = \frac{\ln 2 \cdot \lambda \cdot 100 \cdot 60}{T_{1/2}}$$

$T_{1/2}$ is the halftime of elimination of ^{133}Xe in sec, $\ln 2$ is the natural logarithm of 2. λ represents the partition coefficient of ^{133}Xe between blood and tissue and is dependent on the fat content in the tissue. To determine the fat content, two 0.5 g samples of nasal mucosa (obtained at autopsy) were extracted by homogenization in isopropanol:heptane:sulphuric acid 40:10:1 (v/v/v). After partition against an acidified aqueous phase the isopropanol was evaporated under nitrogen and the weight of the lipid extract determined. The fat content was 1.1 and 1.2 g per 100 g. Hence a value of $0.7 \text{ ml} \cdot \text{g}^{-1}$ was used for the partition coefficient of the nasal mucosa since this value has been used in tissues with low fat content (Lassen et al., 1964; Ladefoged, 1966; Sejrsen, 1971).

RESULTS

1. Disappearance of ^{133}Xe Studied by a Single Scintillation Detector

A typical ^{133}Xe wash-out curve with the injection technique is shown in Fig. 5. The curves were found to be multiexponential and three different components were separated according to Sejrsen (1971). Firstly, the best straight line was drawn for the tail part of the curve and this component was subtracted from the rest of the curve. The line was calculated using a least-squares fit for monoexponential function. Then the second component was subtracted from the residual curve, and finally the first component was obtained. The halftime of elimination was 31 ± 6 , 137 ± 20 and 1430 ± 341 sec (mean $\pm$ SD) for the first, second and third component, respectively. The first wash-out component was concluded within 5–7 min. The recording had to be extended for about 15–20 min before the slope of the wash-out curve straightened out.

Calculated from the initial slope of the first 5 min of the wash-out curve and without sub-

traction of the following components (see Discussion), the blood flow of the reference curves was calculated to $39 \pm 5 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ with a $T_{1/2}$ of $77 \pm 10 \text{ sec}$ (mean $\pm$ SD).

Studies with vasoactive substances

The blood flow (mean $\pm$ SD) calculated from the initial slope was decreased after oxymetazoline ($21 \pm 3 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$) and increased after histamine administration ($52 \pm 7 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$) compared with the reference value ($39 \pm 5 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$). The wash-out curves for the first 15 min are shown in Fig. 2.

Recordings in corpses

From Fig. 2 it can be seen that the ^{133}Xe disappeared very slowly in corpses. The $T_{1/2}$ of ^{133}Xe elimination was about 1600 sec and the two curves were completely coincident.

III. Disappearance of ^{133}Xe Studied by a Scintillation Camera

In the first min about 40% of the injected ^{133}Xe disappeared. Soon after the injection, when the ^{133}Xe activity was high, it was possible to locate the isotope in the nose and to follow its disappearance.

Disappearance by blood flow

In the subjects 79 and 67% respectively, of the ^{133}Xe activity in the mucosa at 1 min was found in the expired air after 5 min. This represented the disappearance from the nasal mucosa by blood flow. Compared with 1 min after the injection, 16 and 28% respectively, of the ^{133}Xe still remained in the mucosa after 5 min. The blood-flow values calculated from scintillation-camera curves were 26 and 18 $\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$, compared with 28 and 20 $\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$, respectively, determined with the single scintillation-detector technique. It should be noted that the blood flow in laryngectomies is lower than in healthy subjects (39 ± 5 , see above).

Disappearance by leakage from the mucosa to the nasal air

The time-activity curve from the carbon-trap showed an exponential leakage of ^{133}Xe from the mucosa to the nasal air. The total leakage from 1–5 min after the injection was only about 5% of the activity at 1 min.

Spreading of ^{133}Xe in the inferior turbinate

The injected ^{133}Xe was found to remain in the mucosa of the inferior turbinate (Fig. 4). The diameter of this area was calculated to be less than 10 mm.

DISCUSSION

After injection of ^{133}Xe into a tissue there is a gradual wash-out of ^{133}Xe . It is well-known that this wash-out is dependent on the blood flow. Various ways have been tried for calculation of the blood flow from the ^{133}Xe wash-out curve. Sejrnsen (1971) found two components in the ^{133}Xe wash-out curve, after labelling the skin, and concluded that they corresponded to the blood flow in different tissues or to the injection trauma. He found that the first slope of the wash-out curve was steeper after injection of the ^{133}Xe in saline solution intracutaneously, than after epicutaneous labelling of ^{133}Xe gas and assumed that the injection trauma caused an increased initial disappearance of ^{133}Xe . Ottesen (1980) studied the myometrial blood flow in rabbits, comparing atraumatic local labelling and local injection of ^{133}Xe . He found, on the other hand, that the average blood flow values were similar with the two methods. In the present investigation we found that in the human nasal mucosa the ^{133}Xe wash-out curve consisted of three different components when it was followed for more than 15 min. Our opinion is that the different components probably do not correspond to blood flow in different vessels or parts of the mucosa. Instead, various other factors could influence the wash-out curve, causing it to depart from linearity. Thus, it could be due to a counter current exchange of

the tracer from venous to arterial blood, to differences in blood flow and/or fat content in the tissue, and/or to the complex anatomy of the vessels in the mucosa of the inferior turbinate.

According to Lassen (1967) one need not subtract the tail part from the ^{133}Xe wash-out curve, and it is the initial slope of the curve that is the important part to be used for mean tissue blood flow calculations. Ladefoged (1966), studying renal blood flow with ^{133}Xe wash-out, reported good agreement between the blood flow calculated from the initial slope of the wash-out curve and from simultaneous measurements with an electromagnetic flowmeter in dogs. He postulated that registration of the wash-out curve for 1–2 min gave sufficient data for calculation of mean blood flow. In an isolated gastrocnemius muscle of the cat, Sejrsen & Tønnesen (1968) compared the direct venous outflow with wash-out curves of ^{133}Xe after atraumatic intra-arterial and local labelling of the muscle. When calculating the blood flow from the initial slope of the wash-out curve, a good agreement between the methods was obtained. Wilson et al. (1975) studied the disappearance of ^{133}Xe from the submucosa of the canine jejunum. Simultaneously, they measured blood flow with a flowmeter applied to the superior mesenteric artery. They assumed that all perfused compartments were represented during the initial rapid wash-out and if the value for the tissue-to-blood partition coefficient was known, the mean blood flow could be calculated directly according to the basic Kety formula (Kety, 1949). Judging from these authors, it may be concluded that the initial slope of the wash-out curve is a fair expression of the blood flow also in the nasal mucosa. Therefore, we propose that the blood flow in the nasal mucosa should be calculated from T_1 of disappearance of ^{133}Xe during the first 5 min without separation of the wash-out curve in different components.

In the present investigation it was found that ^{133}Xe injected into the human nasal muco-

sa disappeared rapidly. In the healthy subjects about 90% (see Fig. 2) of the activity disappeared between 1–5 min. This very rapid elimination of the activity in the mucosa does not upset calculation of blood flow since the tissue-to-blood diffusion equilibrium is reached even at high blood flow rates (Tønnesen & Sejrsen, 1967; Sejrsen & Tønnesen, 1968). Furthermore, the rapid elimination of ^{133}Xe reduces a possible counter current exchange (Tønnesen & Sejrsen, 1970; Sejrsen & Tønnesen, 1972; Ottesen, 1980).

The calculation of the blood flow in the human nasal mucosa from ^{133}Xe wash-out curve may be affected by many factors such as injection trauma and the value of the partition coefficient. The role of the injection trauma was minimized by the cautious injection technique. It seems reasonable to assume that the injection trauma is similar in each experiment. Since it was found that the blood flow increased or decreased after vasoactive substances, it may be concluded that the injection trauma does not invalidate the ^{133}Xe wash-out method when studying blood-flow changes in the nasal mucosa. The partition coefficient, λ , can change somewhat with variations in the haemoglobin content of the blood. In most circumstances, however, correction of λ for haemoglobin content will be insignificant (Sejrsen, 1971).

The regional blood flow is controlled by the resistance vessels while it is not influenced to any appreciable degree of the capacitance vessels (Mellander & Johansson, 1968). The presence of arterio-venous shunts (Rossatti, 1954) may invalidate the calculations of the blood flow (Änggård & Edwall, 1974). The choice of indicator seems to be an important factor in this respect. Kety (1949) used a hydrophilic particle, which does not cross the endothelial membranes readily. This may give too small values of the blood flow. By contrast ^{133}Xe is lipophilic, and lipid cell membranes constitute no barrier for the gas (Lassen et al., 1964). According to Sejrsen (1971) the exchange conditions between the blood in shunt vessels and

the tissue "are essentially of the same nature as those found for arterioles and venules, so that it is possible to imagine that by means of this method, part at least of the blood flow in the shunt vessels is measured". Whether or not the wash-out of ^{133}Xe from the nasal mucosa is influenced by the blood flow in the arterio-venous shunts, cannot be judged by the present study, however.

Determination of the nasal mucosal blood flow by the scintillation camera was in good agreement with that determined by the single collimated detector. The single detector has a much higher sensitivity than the scintillation camera and is to be preferred in ordinary determinations. The scintillation camera was, however, an indispensable tool in the study of special details such as leakage from the mucosa to the nasal air and spreading of the tracer from the injection site in the inferior turbinate. The ^{133}Xe did not spread far from the point of injection in the mucosa. This is an important prerequisite for the method.

The disappearance of ^{133}Xe depends on both blood flow and loss to the air across the surface of the mucous membrane. The experiments on corpses indicated that only a minor part of the ^{133}Xe leaks through the mucosa to the nasal air. This was verified in the experiments on the laryngectomees, who offer an excellent possibility for studying the disappearance of ^{133}Xe in detail, i.e. the part carried away by the blood flow, the leakage from the mucosa to the nasal air, and the spreading of the isotope in the mucosa itself from the site of injection. The part of ^{133}Xe removed by the blood flow from the nasal mucosa should be found in the expired air collected from the tracheostoma since ^{133}Xe is nearly completely eliminated from the blood in one lung passage and recirculation is negligible (Alpert et al., 1968). In the laryngectomees the leakage of ^{133}Xe was found to be very small, and it is likely that the leakage across the mucosal surface is less with increased blood flow and can be considered negligible in ordinary blood-flow determinations. The lymph flow is a pos-

sible source of error, but in relation to the venous outflow, it is probably of no practical importance.

The present data indicate that the disappearance of ^{133}Xe well reflects the mucosal blood flow. It should be stressed, however, that the absolute value of the blood flow may not coincide exactly with the blood flow calculated from the disappearance of ^{133}Xe . The ^{133}Xe wash-out technique will, however, enable us to perform further studies of the nasal blood flow under various physiological and pathological conditions and to study the effect of different drugs applied locally or given systemically.

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ZUSAMMENFASSUNG

Die ^{133}Xe Auswaschtechnik wurde als Methode zur Berechnung der Durchblutung der Nasenschleimhaut benutzt. Das Verschwinden des ^{133}Xe wurde mit Szintillationsdetektoren gemessen. Bei laryngektomierten Patienten liess sich zeigen, dass die Abnahme des ^{133}Xe aus der Mukosa hauptsächlich von der Durchblutung abhing. Ein Verlust von ^{133}Xe aus der Schleimhaut an die Nasenluft war nicht signifikant. Die Abnahmerate auf ^{133}Xe wurde durch Oxymetazoline vermindert, durch Histamin gesteigert. Dies glich sehr den Wirkungen dieser vasoaktiven Pharmaka auf die Durchblutung der Schleimhaut. Die ^{133}Xe -Isotopentechnik bietet sich als einfache Methode zur Veränderungsbestimmung der Durchblutung der Nasenschleimhaut beim Menschen an.

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BLOOD FLOW WITH ^{133}Xe IN HUMAN NASAL MUCOSA IN RELATION TO AGE, SEX AND BODY POSITION

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Abstract. The blood flow in human nasal mucosa was determined using the ^{133}Xe wash-out method in 80 subjects of both sexes. The blood flow was estimated to (mean $\pm$ SD) $33 \pm 10 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$. A correlation was found between decreasing blood flow and increasing age. There was no difference between the sexes. The blood flow was significantly decreased in the sitting position compared to the supine position. In repeated determinations, the first recording did not disturb the second one 15 to 60 min later. The coefficient of variation was estimated to 22%. The investigation gives reference values for further studies of the blood flow in the human nasal mucosa.

The vascular arrangement in the human nasal mucosa is complex (Batson, 1954; Rossatti, 1954; Cauna, 1970) and there is reason to believe that the regulation of the mucosal blood flow is complex as well. The colour and thickness of the mucosa are influenced not only by changes in blood content in the vascular bed but also by variations in blood flow. Thus, the mucosa may be thick and pale, thick and red, thin and pale, or thin and red, depending on dilatation or constriction of different vascular sections.

The blood flow has been studied qualitatively by colour changes, temperature or thermal conductivity (Mudd et al., 1921; Ralston & Kerr, 1945; Cole, 1954; Drettner, 1961; Konno & Togawa, 1979) and by photoelectric plethysmography (Davis & Hertzman, 1957).

The ^{133}Xe wash-out method for quantitative estimations of the blood flow in the human nasal mucosa has been presented in a previous paper (Bende et al., 1982). The aim of this work was to obtain reference values from a

representative group of individuals taking sex and age into consideration. This is mandatory for further studies of various physiological and pathological conditions. Furthermore, the purpose was to study the possible effect of body position on the blood flow of the nasal mucosa and to test the reproducibility of the method.

MATERIAL

The material consists of 80 persons, 42 men and 38 women. The mean age for both men and women was 44 years range 21–80 and 20–84, respectively (Fig. 1).

The subjects were either patients at an Ear, Nose and Throat Clinic ($n=19$), being hospitalized for ailments other than those of the respiratory tract (e.g. vertigo, benign salivary gland tumours and oesophageal diverticula) or healthy volunteers ($n=61$). Only non-smokers without symptoms from the respiratory tract and with normal rhinoscopic findings were accepted for the investigation. Cases with suspected or known allergic or vasomotoric rhinitis were excluded. None were under any medication known to influence the nasal mucosa. Persons with hypertension were excluded. The following criteria for hypertension were used:

>60 years: systolic blood pressure (b.p.) >180 and/or diastolic b.p. >105,

40–60 years: systolic b.p. >170 and/or diastolic b.p. >100,

<40 years: systolic b.p. >160 and/or diastolic b.p. >90.

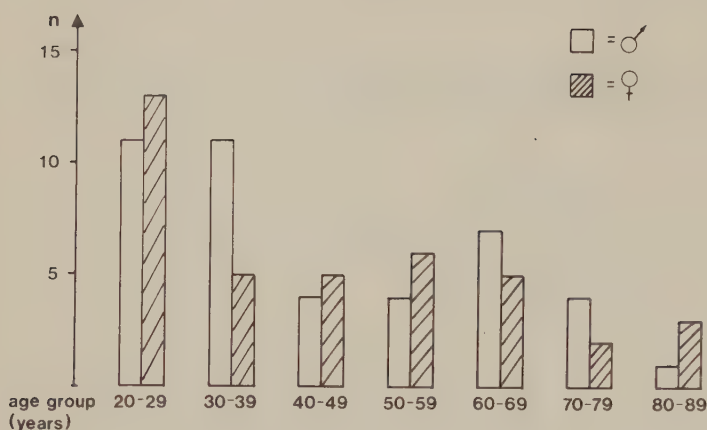


Fig. 1. Distribution according to age and sex.

METHOD AND PROCEDURE

Quantitative blood-flow determinations were made by the ^{133}Xe wash-out method described in detail by Bende et al. (1982). 0.1 ml of ^{133}Xe in an isotonic NaCl solution, containing an activity of 1–10 MBq was injected into the mucosa in the anterior and medial part of the right inferior turbinate. A scintillation NaI-(Tl)-detector (diameter 50×10 mm) with a collimator (diameter and depth 50 mm) connected to a scaler-timer was used for the recordings. The detector was placed over the nose (Fig. 2). Blood pressure and pulse-rate were measured in all subjects. The number of pulses after injection of ^{133}Xe into the mucosa were determined over a 10 s interval every 30 s for 5 min. All figures were corrected for background and analyzed by a computer using a least-squares fit for a monoexponential function (Fig. 2). The line of the wash-out curve for 1–5 min after the injection of ^{133}Xe was drawn and $T_{1/2}$ (s) was determined. The computer calculated the blood flow (f) in $\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ from the equation:

$$f = \frac{\ln 2 \cdot \lambda \cdot 60 \cdot 100}{T_{1/2}}$$

where λ represents the partition coefficient of ^{133}Xe between blood and tissue and a value of 0.7 $\text{ml} \cdot \text{g}^{-1}$ was used.

In 10 subjects (4 men and 6 women, age

21–59 years, mean age of 38 years) the effect of body position on blood flow was tested. After one recording in the supine position, a second recording was performed in the sitting upright position with the head fixed.

In 28 subjects (13 men and 15 women, age 21–78 years, mean age of 39 years) the reproducibility of the method was tested in double recordings with an interval of 15–60 min and using the same nasal cavity. If necessary, the background from the foregoing recording was measured and corrected for with a supposed $T_{1/2}$ of 1000 s. From previous investigations (Bende et al., 1982) it was found that the ^{133}Xe

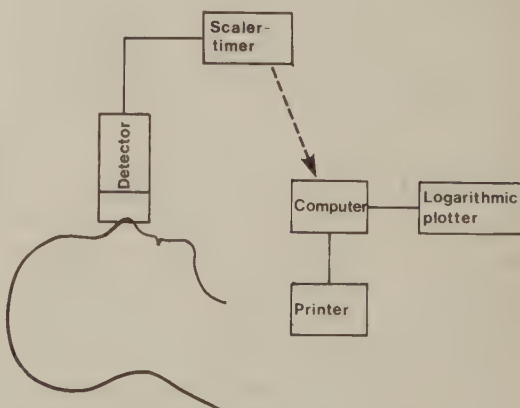


Fig. 2. Block diagram of the experimental device. All values are fed to the computer for listing of blood flow on the printer and drawing of the wash-out curve on the plotter.

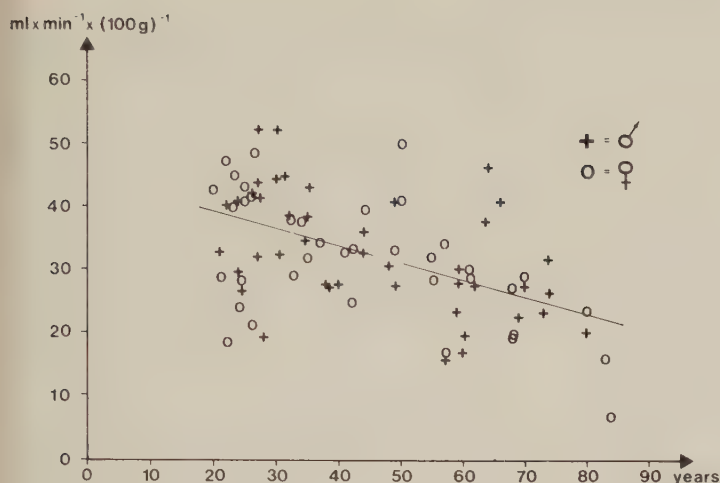


Fig. 3. Nasal mucosal blood flow (in $\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$) versus age in 80 subjects (42 men and 38 women). Line of regression ($y = -0.27x + 44.68$) is indicated.

wash-out curve straightened out after 15 min with a $T_{1/2}$ of about 1000 s.

Initially, 27 subjects (12 men and 15 women, age 21–73 years, mean age of 38 years) were investigated in order to determine whether mouth- or nose-breathing had any effect on the recordings. In double recordings, nose-breathing was performed first in 17 and mouth-breathing first in 10 determinations, with an interval of 15–30 min. Since there was no difference (see below) the subjects taking part in the further investigations were told to breathe the way they preferred.

For statistical evaluation *t*-test for paired and unpaired data was used. *P*-values smaller than 0.05 were considered significant.

RESULTS

Blood flow (mean $\pm$ SD) in the whole material ($n=80$) was $33 \pm 10 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$. Blood flow in men ($n=42$) and women ($n=38$) were 34 ± 10 and $32 \pm 10 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (mean $\pm$ SD), respectively. There was no statistically significant difference in blood flow between men and women.

A relationship was found between age and blood flow. With increasing age, the blood flow decreased. At 20 years the mean blood flow was about 39 and at 80 years about 23

$\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$. The coefficient of correlation (*r*) for blood flow versus age was -0.51 and the regression was expressed as $y = -0.27x + 44.68$. No statistically significant difference was found between males and females regarding the correlation for blood flow and age. In Fig. 3 the blood flow versus age in the whole material is plotted and the line of regression indicated.

The values (mean $\pm$ SD) for the blood flow in the supine and sitting position were 35 ± 7.5 and $29 \pm 9.5 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$, ($n=10$), respectively. This difference is statistically significant at a level of $p < 0.05$.

In double recordings ($n=28$), in order to test the reproducibility, the difference was $0.6 \pm 10 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (mean $\pm$ SD). This difference was not statistically significant. The standard error of a single determination estimated from duplicate determinations expressed as the coefficient of variation according to Dahlberg (1940) has been calculated to 22%.

For 17 subjects, where nose-breathing preceded mouth-breathing, the mean $\pm$ SD difference in blood flow was $-1.5 \pm 10 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$. In 10 additional subjects, where mouth-breathing preceded nose-breathing, the mean difference was -0.6 ± 9 . The differences within each category and be-

tween the means were not found to be significant.

DISCUSSION

It is known that sex differences exist concerning other physiological parameters and changes in nasal patency can be related to the hormonal state (Taylor, 1973; Postema et al., 1980). Therefore it is interesting that this investigation did not show any difference between men and women regarding nasal mucosal blood flow.

Studying the nasal resistance with rhinomanometry, Hasegawa & Kern (1977) found an increased nasal patency in subjects over 40 years and the nasal cycle was less prominent. With aging there is also an increased atrophy of the mucosa (Wustrow, 1958) and a decreased vascular elasticity (Somlyo & Somlyo, 1968). The correlations between age and blood flow in this study support the previous findings.

In a study, using temperature changes in the nasal mucosa as an indicator, Allen et al. (1965) supposed that changes in body position caused alterations in the *blood flow*. This is more directly verified by the present investigation and the decreased nasal mucosal blood flow in the sitting position compared to the supine position might be due to a diminished perfusion pressure. The *blood content* in the human nasal mucosa is also thought to change with the body position in patients with acute rhinitis (Rundcrantz, 1969) and in normal subjects (Winslow et al., 1934; Aust & Drettner, 1975; Broms, 1980; Jannert, 1982). But this is due to changes in the capacitance vessels and the fact that the veins in the upper part of the body have no valves.

There seem to exist spontaneous and relatively regular variations in the human nasal mucosal blood flow, and there are findings indicating that also emotional factors might influence the blood flow (Drettner, 1961). Peripheral vascular functions are actively controlled by adjustments of the level of tone in

the different vessels (Zweifach et al., 1953; Mellander & Johansson, 1968). Adjustments of tone in the resistance vessels may contribute to the variations of nasal mucosal blood flow found in the repeated determinations of this study. The coefficient of variation (22%) is, however, about the same as in studies in other tissues using the ^{133}Xe wash-out method. Thus in muscle, Lassen (1967) reported a variation of 15–20% in two determinations in the same patient, and Tønnesen (1969) reported a coefficient of variation of 33% with recordings in different days. The large coefficient of variation in this work can, however, be explained by error of the method as well as by actual changes in blood flow or a combination of both. While it is of interest to further investigate and evaluate these variations the diagnostic value of the method will not be improved until either separate reference values can be obtained for specific physiological conditions or the test conditions are standardized to a specific, preferred physiological status of the patient. For example, the so-called "nasal cycle" with known cyclic variations of the blood content in human nasal mucosa, which are well-known from rhinomanometric studies (Heetderks, 1927; Stoksted, 1952; Keuning, 1968; Hasegawa & Kern, 1977), may be accompanied by cyclic blood-flow changes as well. It might be possible to perform blood-flow determinations in a certain phase of the "nasal cycle", using rhinomanometry in combination with the ^{133}Xe wash-out technique, but this seems to afford great technical difficulties.

Although the coefficient of variation was relatively large, the differences in repeated estimations were about equally distributed above and below the mean, indicating that the first determination did not disturb the second. This also indicates that the trauma caused by the injection is of minor importance. The values of the nasal mucosal blood flow obtained in this study can be used as reference values in further studies with the ^{133}Xe wash-out technique in different disorders of the upper respi-

ratory region and for investigations of effects of various drugs on nasal mucosal blood flow.

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ZUSAMMENFASSUNG

Mit Hilfe der ^{133}Xe -Isotop-Technik wurde die Durchblutung der menschlichen Nasenschleimhaut bei 80 Individuen beider Geschlechter bestimmt. Der Blutfluß (Mittel $\pm$ SD) betrug $33 \pm 10 \text{ ml} \cdot \text{Min}^{-1} \cdot (100 \text{ g})^{-1}$. Es wurde eine Korrelation zwischen verminderter Durchblutung und zunehmendem Alter gefunden. Es bestanden keine geschlechtlichen Unterschiede. In sitzender Stellung war die Durchblutung im Vergleich zu liegender Stellung signifikant vermindert. Die Standardabweichung einer Einzelbestimmung betrug 22%. Bei Doppelbestimmungen beeinflusste die erste Messung die zweite, die 15 bis 60 Minuten später vorgenommen wurde, nicht. Diese Untersuchungen geben Bezugswerte für weitere Studien der Durchblutung menschlicher Nasenschleimhaut.

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BLOOD FLOW IN HUMAN NASAL MUCOSA AFTER TOTAL LARYNGECTOMY

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Abstract. The blood flow in the human nasal mucosa was determined in 10 laryngectomees with the ^{133}Xe wash-out method. The blood flow was estimated to be $19.3 \pm 2.1 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (mean $\pm$ SEM) which is significantly lower than in healthy non-laryngectomees. The decreased blood flow could be one of the explanations of the functional and morphological alterations in the nasal mucosa after total laryngectomy.

Certain changes seem to take place in the nasal mucosa after total laryngectomy. It appears to be more violet in colour, suggesting changes in the vascular bed (Sternberg, 1924; Dixon et al., 1949; Schwab, 1955). Functional changes occur and the normal nasal cycle, with periods of changing blood content in the mucosa, is found to disappear (Keuning, 1968). Also morphological findings with microscopic changes in arterioles and capillaries after laryngectomy or permanent tracheostomy have been described by some authors (Sternberg, 1924; Topozada & Gaafar, 1976), while others (Dixon et al., 1949; Schwab, 1955) have failed to demonstrate such changes.

The ^{133}Xe wash-out method (Bende et al., 1982) makes it possible to estimate the blood flow in the human nasal mucosa. The aim of this investigation was to study the blood flow in the nasal mucosa after total laryngectomy and compare the values with those of normal subjects.

MATERIAL AND METHOD

Ten laryngectomees (9 men and 1 woman, aged 55–79 years, average 72 years) were examined. All had been submitted to total laryngectomy

and the time elapsing since operation was 1 to 20 years, average 10 years. One patient had an early recurrence in the stoma and one suffered from cancer of the prostate without actual problems, but the others were without signs of recurrent tumour and in good health. None were on medication known or suspected to influence the nasal mucosa.

The laryngectomees were compared with matched pairs of 10 healthy subjects (6 men and 4 women, aged 55–80 years, average 72 years). They were all non-allergic and without symptoms from the respiratory tract.

In an additional comparison, the laryngectomees were compared to a previously published reference material (Bende, 1982) of 80 healthy subjects (42 men and 38 women, aged 24–84 years, average 42 years). Since there was a correlation between blood flow and age in that material, the difference in age between the reference group and the laryngectomee group was corrected for with a prediction method according to Draper & Smith (1980).

For statistical evaluation, the *t*-test for unpaired data was used. *p*-Values smaller than 0.05 were considered significant.

The blood flow in the nasal mucosa was determined with the ^{133}Xe wash-out method as previously described (Bende et al., 1982). Thus, 0.1 ml ^{133}Xe saline solution containing 1–10 MBq was injected into the mucosa of the inferior turbinate and the elimination of the isotope was followed with a scintillation detector. The blood flow was calculated from the initial slope of the first 5 min of the wash-out curve.

RESULTS

In all laryngectomees, the nasal mucosa appeared thin and was slightly bluish in colour at anterior rhinoscopy. The blood flow in the mucosa was determined to $19.3 \pm 2.1 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (mean $\pm$ SEM). For individual values, see Table I. In the matched pairs of healthy non-laryngectomees, the blood flow was $26.7 \pm 1.8 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$. The difference is statistically significant ($p < 0.005$).

After correction for differences in age between the laryngectomees and the reference group, the blood flow of the reference material was $25.3 \pm 1.3 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (mean $\pm$ SEM). This is significantly higher than that in the laryngectomee group ($p < 0.05$).

A correlation between age and blood flow was found in the laryngectomees, so that with increasing age the blood flow decreased. The coefficient of correlation (r) for blood flow versus age was -0.43 . The regression equation was $y = -0.40x + 48.44$. After correction for age, no correlation was found between blood flow and time since operation.

DISCUSSION

The main functions of the human nasal mucosa are heating, moistening, and cleaning of the inspired air during its passage to the lower airways (Proetz, 1953). It has been proposed that the nasal mucosa also is involved in the regulation of body temperature (Cole, 1954; Scott, 1954; Cramer, 1957). The respiratory air current through the nose is also important in olfaction. After laryngectomy, these nasal functions are discontinued, with the abolished air current. Several authors have observed alterations in the nasal mucosa after laryngectomy. Thus, morphologically, the mucosal colour changes from normal pink to more violet (Ritter, 1964; Henkin & Larson, 1972), squamous epithelium is in some areas of the mucosa gradually replaced by ciliated columnar epithelium (Dixon et al., 1949), and

Table I. Blood flow in the nasal mucosa in laryngectomees, using the ^{133}Xe wash-out technique

Sex	Age (years)	Post-operative time (years)	Blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$)
m	55	19	23.2
m	67	1	27.4
f	70	4	21.4
m	70	17	20.5
m	73	11	21.4
m	75	18	13.8
m	75	2	18.6
m	78	20	19.2
m	79	2	16.0
m	79	1	11.9
Mean $\pm$ SE	72	10	19.3 ± 2.1 ($n=10$)

changes in the vascular bed and the connective tissue have been described (Sternberg, 1924; Dixon et al., 1949; Topozada & Gaafar, 1976). Functionally, the so-called nasal cycle is abolished (Keuning, 1968), a decreased olfactory acuity is found (Dixon et al., 1949; Ritter, 1964; Henkin & Larson, 1972), and the surface temperature of the mucosa is higher than in normals (Dixon et al., 1949; Schwab, 1955). It is not clear, however, what mechanisms are responsible for the morphological and functional alterations found after laryngectomy. For example, there is a disagreement concerning the cause for the hyposmia, which is not necessarily due to morphological changes. Ritter (1964) has shown that the power of olfaction did not change in laryngectomees, and assumed that the abolished air current was the only factor in hyposmia. Alterations of the vascular function in the nasal mucosa have been discussed as a cause for the morphological and functional changes after laryngectomy (Sternberg, 1924; Dixon et al., 1949; Keuning, 1968; Henkin & Larson, 1972; Stell, 1981), supported by microscopic findings in arterioles and capillaries (Sternberg, 1924; Topozada & Gaafar, 1976). However, the blood flow in the human nasal mucosa after total laryngectomy has not been evaluat-

ed so far. The present results with a decreased blood flow after total laryngectomy, in comparison with non-laryngectomees, are therefore illustrative, and could be a contributory cause for the morphological and functional changes occurring after total laryngectomy. There was no correlation in this study between the decreased blood flow and time since operation. This indicates that the changes might occur early after laryngectomy, at least within the first year.

ZUSAMMENFASSUNG

Der Blutfluss der menschlichen Nasenschleimhaut wurde in 10 laryngektomierten Patienten mit Hilfe der ^{133}Xe Isotop-Technik bestimmt. Der Blutfluss (Mittel $\pm$ SEM) betrug $19.3 \pm 2.1 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$. Dies bedeutet eine signifikante Herabsetzung der Durchblutung im Vergleich zu gesunden nicht-laryngektomierten Personen. Die verminderte Durchblutung konnte früher beschriebene morphologische Veränderungen der Nasenschleimhaut erklären.

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THE EFFECT OF TOPICAL DECONGESTANT ON BLOOD FLOW IN NORMAL AND INFECTED NASAL MUCOSA

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Abstract. The nasal mucosal blood flow was determined by means of the ^{133}Xe wash-out method in an early stage of acute rhinitis and in health and the effect of a topical decongestant (oxymetazoline) was evaluated. During an early stage of acute rhinitis, a statistically significant increase of blood flow was found. The topical decongestant in therapeutically recommended doses decreased the blood flow significantly in acute rhinitis as well as in healthy subjects. The effect was more pronounced in acute rhinitis. The effect of oxymetazoline was dose dependent and a statistically significant decrease was found in doses of about 1/50 of the therapeutically recommended. The clinical implication is that it might be possible to reduce the dose of the decongestant in order to minimize the negative side effect of a decreased blood flow.

Common cold with acute rhinitis is one of the most frequent diseases in man. The different pathophysiological mechanisms involved in the infected nasal mucous membrane are not yet completely known. The treatment is symptomatic and the drugs most frequently used are topical decongestants.

Topical decongestants are sympathomimetic drugs with a documented constricting effect on the capacitance vessels (Weiner, 1980), resulting in a decongestion of the nasal mucosa which reduces the nasal airway resistance and thereby facilitates nose-breathing. Very little is known, however, about the effect of topical decongestants on the resistance vessels controlling the blood flow in the nasal mucosa.

This study was designed to investigate the effect of topical decongestants on nasal mucosal blood flow in acute infectious rhinitis and in health using the ^{133}Xe wash-out method (Bende et al., 1982).

MATERIAL

In 18 healthy subjects (5 men and 13 women, aged 18–25 years, mean age 27) the nasal mucosal blood flow was recorded before and after application of a topical nasal decongestant substance. The effect of placebo was studied in 3 of the subjects (women, aged 20, 25 and 28 years). All subjects had normal rhinoscopic findings and none was on medication known to have any effect on the nasal mucosa at the time of the investigation.

Eight of the 18 subjects (2 men and 6 women, aged 18–32 years, mean age 25) were also tested during an early stage (the first 2 days) of an acute infectious rhinitis, before and after application of a topical decongestant. All had a red and swollen nasal mucosa with mucoid or mucopurulent discharge, verified by anterior rhinoscopy. None had used, within 24 hours, any decongestant or drugs known to interfere with nasal blood flow.

Five of the 18 subjects (all women in healthy condition, aged 20–28 years, mean age 24) were also investigated with decongestant in different doses.

METHOD AND PROCEDURE

The nasal mucosal blood flow was determined with the ^{133}Xe wash-out method (Bende et al., 1982). Thus, 0.1 ml ^{133}Xe in saline solution containing 1–10 MBq was injected into the mucosa of the inferior turbinate and the elimination of the isotope was followed with a scintillation detector. The blood flow was cal-

Table I. Blood flow (mean $\pm$ SEM) in the nasal mucosa $\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ in 8 subjects, investigated in health and during acute rhinitis before and after application of topical decongestant (oxymetazoline)

Healthy condition			Acute rhinitis		
Before	After	Decrease (%)	Before	After	Decrease (%)
42	17	60	39	19	51
49	20	59	45	28	38
46	35	24	63	24	62
38	20	47	58	19	67
39	23	41	55	26	53
36	25	31	47	26	45
33	18	45	42	15	64
44	21	52	50	30	40
41 $\pm$ 2	22 $\pm$ 2	45	50 $\pm$ 3	23 $\pm$ 2	53

culated from the initial slope of the first 5 min of the wash-out curve.

Oxymetazoline chloride (Nezeril[®], Draco, Sweden) was used as nasal decongestant. In all subjects blood flow had been estimated without the influence of any drug and 15 min after drug application of three drops (0.1 ml) on the inferior turbinate of oxymetazoline (0.5 $\text{mg} \cdot \text{ml}^{-1}$) which is the clinically recommended dose. The subjects were in the supine position for 2 min after instillation of the decongestant. In three subjects 0.1 ml placebo-Nezeril[®] was used instead of oxymetazoline.

The effect on the blood flow of oxymetazoline in five different concentrations (from 0.01 to 3 $\text{mg} \cdot \text{ml}^{-1}$), but in the same amount of solution, was studied on different days in 5 subjects. The blood flow without oxymetazoline was estimated 3 to 4 times in every subject and the mean value was used for comparison.

For statistical evaluation the *t*-test for paired data was used. *p*-Values smaller than 0.05 were considered significant.

RESULTS

In health the nasal mucosal blood flow was estimated to $40 \pm 2 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$

(mean $\pm$ SEM, $n=18$). Oxymetazoline decreased the blood flow in all subjects and the blood flow was $23 \pm 3 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$, corresponding to a decrease of 43% (Fig. 1 A). The difference is statistically significant ($p < 0.001$). By anterior rhinoscopy a decongestive effect was observed in all subjects. After administration of placebo-Nezeril[®] the blood flow increased in two subjects by 7 and 11 $\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$, respectively, and decreased in one subject by 2 $\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$.

In acute rhinitis the blood flow was estimated to $50 \pm 3 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (mean $\pm$ SEM, $n=8$). During health the blood flow of the same 8 subjects was $41 \pm 2 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (Table I). This means that the blood flow increased by 22% during acute rhinitis. The difference is statistically significant ($p < 0.05$).

In acute rhinitis administration of oxymetazoline decreased the blood flow to $23 \pm 2 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$, which is a decrease of 53% (Table I). During health the blood flow decreased from 41 ± 2 to $22 \pm 2 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ as an effect of oxymetazoline (Table I). This is a decrease of 45%. The effect of oxymetazoline is statistically significant ($p < 0.001$).

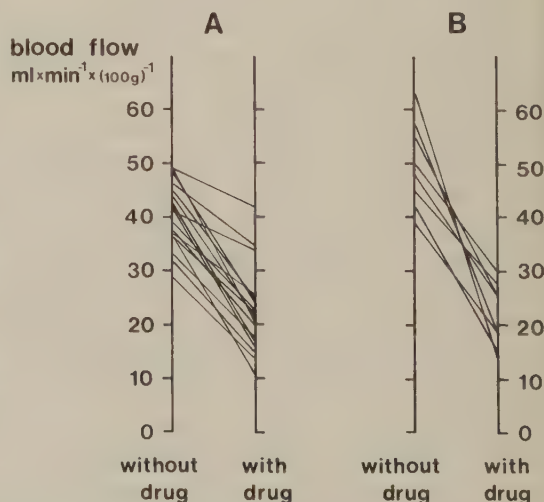


Fig. 1. Nasal mucosal blood flow before and after a topical nasal decongestant (oxymetazoline) in health (A, $n=18$) and in subjects with acute rhinitis (B, $n=8$).

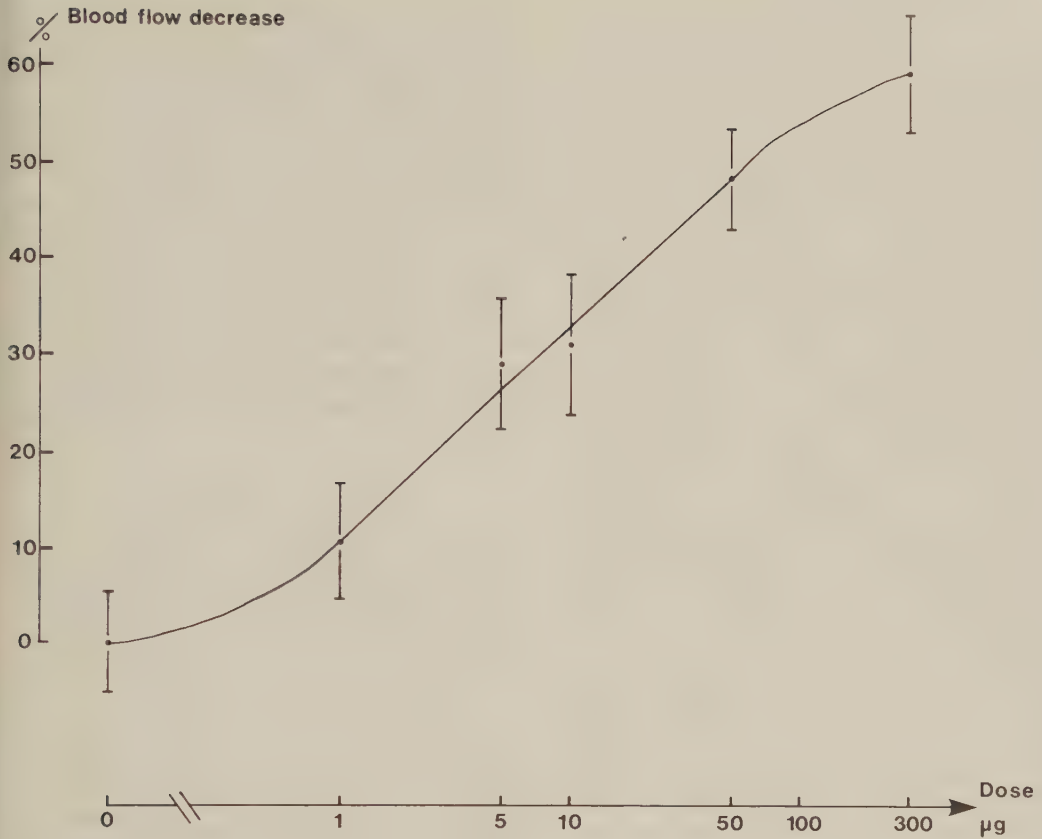


Fig. 2. Semilogarithmic relationship between different doses of oxymetazoline and nasal mucosal blood flow (mean $\pm$ SEM) in five healthy subjects.

in both health and during acute rhinitis. The blood flow was decreased to about the same level in both conditions, although the starting values before administration of oxymetazoline was higher in acute rhinitis (Fig. 1 A and 1 B).

With increasing doses of oxymetazoline the blood flow decreased in a dose-response relationship (Fig. 2). The effective dose giving 50% of the maximum response (ED_{50}) is about 10 μ g (Fig. 2). There is a statistically significant decrease in blood flow already after application of 1 μ g oxymetazoline ($p < 0.05$).

DISCUSSION

Oxymetazoline is a sympathomimetic drug with specific α -adrenoceptor stimulating effect

(Hotovy et al., 1961; Mujić & van Rossum, 1965) with preference for α_2 -receptors (Starke et al., 1975; Andersson, 1980). It is a potent vasoconstrictor agent and in common clinical doses it is an effective nasal decongestant without systemic effects (Miodek, 1962; Green, 1966; Connell, 1969; Cohen & Duffy, 1969). With a related decongestant drug, xylo-metazoline, the vasoconstrictor effects on nasal blood vessels have been evaluated in man by studying temperature changes of the nasal mucosa (Biesalski & Marquardt, 1959) and in animal experiments in vitro (Jackson, 1979) and in vivo (Naumann, 1961). Naumann found that the arterioles and the precapillary sphincters were more sensitive to sympathomimetic drugs than the veins. Differences in sensitivity

between the resistance vessels and the capacitance vessels have not been evaluated in the present study.

Drettner (1961) studied the blood flow in human nasal mucosa during common cold by means of temperature changes and found somewhat higher temperature in the mucosa compared to normal conditions but the difference was not statistically significant. In the present study a statistically significant increase of the nasal mucosal blood flow was found in acute rhinitis, which supports Drettner's findings.

Naumann (1961) found that the vessels in the "irritated nasal mucosa" of the rabbit were less reactive to vasoactive substances than the vessels in the normal mucosa. He therefore questioned the effect of sympathomimetic drugs in acute rhinitis. The present investigation shows, however, that the effect of oxymetazoline on the nasal blood flow was more pronounced in acute rhinitis than in health. As an increased blood flow is a part of the inflammatory reaction—and thereby also of advantage for the local tissue defence against infection—it is not entirely satisfying to decrease the blood flow by using topical decongestants. Theoretically, a decreased blood flow might delay the healing of the infection in the nasal mucosa and several authors have for different reasons expressed some hesitation about the use of decongestants (Änggård, 1974; Proctor & Adams, 1976; Mygind, 1978; Peerless & Noiman, 1980; Talaat et al., 1981). However, the advantage of an improved nose-breathing probably outweighs the effect of the decreased blood flow (Bertler & Drettner, 1967). By keeping the nasal airway open, the air conditioning capacity is to a certain degree maintained and the so-called "Toynbee effect" with a negative intratympanic pressure is avoided.

The topical decongestant oxymetazoline was thus found to be a potent vasoconstrictor substance inducing a statistically significant reduction of blood flow in the nasal mucosa already in doses of 1 µg, i.e. 1/50 of the ap-

proximate therapeutically recommended dose with commercially available oxymetazoline decongestants. It may therefore be possible to attain a clinically sufficient decrease of the nasal airway resistance by lower doses of oxymetazoline than we use today, thereby minimizing the negative effect of a reduced blood flow discussed above. First, however, the decongestive effect on the nasal mucosa must be evaluated and it is not known if the capacitance vessels are as sensitive as the resistance vessels to oxymetazoline, since no dose-response study regarding the capacitance function has yet been published.

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ZUSAMMENFASSUNG

Die Blutströmung in der Nasenschleimhaut wurde, mit Hilfe der ^{133}Xe Auswasch-Methode, teils im Anfang eines akuten Schnupfens, teils bei Gesunden gemessen, und die Wirkung eines örtlichen Entschwellungsmittels (Oxymetazoline) ausgewertet. Im Anfang des akuten Schnupfens wurde eine statistisch sichergestellte Erhöhung der Blutströmung festgestellt. Das örtliche Entschwellungsmittel verminderte die Blutströmung signifikant sowohl bei den Gesunden als auch bei den Patienten mit Schnupfen. Die Wirkung war stärker beim Schnupfen. Die Wirkung von Oxymetazoline war von der Dosis abhängig und eine statistisch sichergestellte Verminderung der Blutströmung wurde bei einer Dosis entsprechend 1/50 der empfohlenen festgestellt. Die klinische Folgerung ist, dass es möglich ist die Dosis des Entschwellungsmittels zu verkleinern, um die negative Nebenwirkung der verminderten Blutströmung auf ein Mindestmass zu beschränken.

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THE EFFECT OF PROVOKED ALLERGIC REACTION AND HISTAMINE ON NASAL
MUCOSAL BLOOD FLOW IN HUMANS

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ABSTRACT

The allergic reaction in the nasal mucosa is a complex pathophysiological process with several chemical mediators involved. One of the primary mediators is histamine. This investigation was performed to study separately the effects of an allergic reaction and of histamine on the human nasal mucosal blood flow with the ^{133}Xe wash-out method. An allergic reaction was provoked by pollen allergens and blood flow was estimated before and after provocation. In healthy subjects and in subjects with allergic rhinitis and off pollen season, the effect of histamine injected into the mucosa was studied. The allergic reaction decreased the blood flow but histamine had an opposite effect in the allergic as well as in the normal subjects. This indicates that histamine alone is not responsible for the vascular effects in allergic rhinitis. Different mechanisms responsible for the decreased blood flow in the allergic reaction are discussed.

INTRODUCTION

Allergic rhinitis is characterized by obstruction, hypersecretion, itching and sneezing and is often combined with eye symptoms. The pathophysiological changes in the mucosa consist essentially of dilation of sinusoids and a marked oedema due to an increased capillary permeability (Mygind, 1978).

The allergic reaction induces a release of chemical mediators from mast cells in the tissue and basophils in the blood. The primary mediators released are histamine, leucotriens, eosinophil chemotactic factor and platelet activating factor. Secondarily, prostaglandins, serotonin and kinins are released, influencing the nasal mucosa in a complex way (Grobler, 1966; Jackson & Burson, 1977; Mygind, 1978). Although the separate effect of some of the mediators on blood vessels can be fairly well predicted, the complex effect of the allergic reaction on the blood flow cannot be predicted.

The aim of this investigation was to study the blood flow in the nasal mucosa in humans during a provoked attack of allergic rhinitis and to study separately the effect of histamine on the mucosal blood flow in allergics out of pollen season and in healthy, non-allergic subjects.

MATERIAL AND METHOD

The investigation was performed on 27 subjects (9 men and 18 women, age 16 to 62 years, average age 29 years). Among these, 17 (6 men and 11 women, average age 24 years) suffered from seasonal allergic rhinitis (pollinosis) and 10 subjects (3 men and 7 women, average age 38 years) were healthy non-allergics.

Clinical examination by rhinoscopy revealed no nasal pathology in any of the subjects before the blood flow recordings. The allergic subjects had no actual symptoms and were examined off pollen season. They had all previously been examined with skin prick test and were positive for the individual allergen used in this study.

The blood flow in the nasal mucosa was determined with the ^{133}Xe wash-out method (Bende et al., 1982). Thus, 0.1 ml of ^{133}Xe in saline solution containing 1-10 MBq was injected into the mucosa of the inferior turbinate and the elimination of the isotope was followed with a scintillation detector. The blood flow was calculated from the initial slope of the first 5 min of the wash-out curve.

The effect of an allergic reaction on blood flow was tested in 10 of the subjects with allergic rhinitis (3 men and 7 women, average age 26 years). Two determinations were performed with an interval of 30 min, the first determination before and the second 15 min after the provocation with the allergen. The maximum allergic reaction is reached after this time (Pelikan & de Vries, 1974). The allergens were sniffed, except for rye-grass, of which a solution was softly applied on the inferior turbinate. The provocation was made according to our clinical routine and not with an exactly known amount of pollen.

The effect of histamine dihydrochloride on nasal mucosal blood flow was tested in the 10 non-allergic subjects and in 10 of the subjects with allergic rhinitis (5 men and 5 women, average age 25 years). After recording the blood flow without influence of any drug, the blood flow after injection of the same amount of xenon-solution containing 20 ug histamine was recorded.

To find out if the nasal mucosal blood flow in the allergic subjects without symptoms differed from the blood flow in non-allergics, a comparison was made between the 17 allergic subjects and a reference material of 80 healthy subjects (Bende, 1982a). Since there was a correlation between blood flow and age in this material, correction was made for the difference in age between the two groups, using a prediction method according to Draper & Smith (1980).

Statistical analyses were performed with paired and unpaired t-test. P-values smaller than 0.05 were considered significant.

RESULTS

After provocation all allergic subjects developed in a few minutes symptoms of an allergic reaction in the nasal mucosa, i.e. obstruction, hypersecretion and sneezing. Some also experienced itching in the nose or pharynx and conjunctival symptoms. Visually the mucosa was swollen and pale-bluish with a watery discharge in all cases. It was noted that the injection trauma after the pollen provocation occasionally caused a small bleeding for some minutes.

The blood flow of the allergic subjects ($n=17$) without symptoms was $41 \pm 2 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (mean $\pm$ SEM). No statistically significant difference was found in blood flow between the allergics and the reference material of healthy subjects after correction for age ($38 \pm 1 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$). After allergen provocation the blood flow of the nasal mucosa decreased in all allergic subjects ($n=10$) from 42 ± 2 to $26 \pm 3 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (mean $\pm$ SEM) (Table I). The difference is statistically significant ($p < 0.001$).

After injection of histamine the blood flow increased in all subjects except one of the allergics (Table II). The blood flow of the allergic subjects ($n=10$) was 39 ± 2 before and $58 \pm 2 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (mean $\pm$ SEM) after histamine injection. In the non-allergic subjects ($n=10$) the blood flow was 34 ± 2 before and $58 \pm 2 \text{ ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$ (mean $\pm$ SEM) after histamine injection. The difference is statistically significant for both groups ($p < 0.001$).

DISCUSSION

In the present study a markedly decreased blood flow in the nasal mucosa was found as a result of the allergic reaction, while locally injected histamine produced an increased blood flow. This emphasizes that in the allergic reaction more factors than histamine are responsible for the vascular reactions.

Histamine has a well known vasodilating effect in the nasal mucosa in animal experiments. This has been shown for the capacitance vessels in the cat (Malcomson, 1959; Hiley et al., 1978) and for the resistance vessels in the dog (Clairmont et al., 1973). In this study - as far as we know for the first time - the vasodilating effect of histamine on the resistance vessels in the human nasal mucosa is shown.

No difference in blood flow was obtained in this study between allergic subjects without symptoms and healthy non-allergic subjects. This supports the result in a recently presented study (Tanimoto et al., 1982) where the nasal mucosal blood flow was determined in healthy and allergic subjects by means of the hydrogen clearance method, previously presented by Aukland et al. (1964). With this method, the nasal blood flow was also investigated by Konno et al. (1982 a) and by Tanimoto et al. (1982) during a provoked attack of allergic rhinitis after application of antigen discs of filter paper on the inferior turbinate in allergic subjects. Konno et al. reported an increased blood flow bilaterally in the inferior turbinates after unilateral provocation, while Tanimoto et al. found an increased mucosal blood flow in the area at some distance from the disc but a decreased blood flow near the area of contact of the allergen disc. The differences in blood flow between the ^{133}Xe wash-out method and the hydrogen clearance method after allergen provocation is difficult to explain and needs further evaluation.

The blood flow values calculated from the hydrogen clearance method were in normals as well as in allergics twice to three times as high as ours. The hydrogen method implies that a sharp electrode is placed deep in the mucosa and is left in situ during the whole recording. This continuous trauma probably causes disturbances in the blood flow and it seems likely that the hydrogen clearance method overestimates peripheral blood flow. This assumption is further supported by the fact that Konno et al. (1982 b) found values of blood flow with the hydrogen clearance method in the skin about twice as high as those with ^{133}Xe wash-out method as measured at room temperature

(Sejrsen, 1969; Daly & Henry, 1980). However, higher blood flow values were obtained with increasing environmental temperature (Palmer, 1972; Daly & Henry, 1980). Compared to another method, labelled microspheres, the skin blood flow calculated from the hydrogen clearance method is about seven times higher (Hof, 1982). We therefore believe that the ^{133}Xe wash-out method is less traumatic and thereby more physiological and reliable, although the calculated blood-flow-value may not coincide exactly with absolute value.

Two types of inflammatory reaction in the human nasal mucosa can be distinguished: the red, swollen mucosa with increased blood flow in acute infectious rhinitis (Bende, 1982 b), and the bluish, swollen mucosa with decreased blood flow in allergic rhinitis. The reason for the decreased blood flow in the allergic reaction is not clear but three main mechanisms could be responsible, either separately or in combinations.

In the allergic reaction an intravascular aggregation of blood cells occur in the capillary bed (Naumann, 1961; Ingelstedt & Rundcrantz, 1964; Terrahe et al., 1970). Intravascular aggregation has been found to decrease blood flow in peripheral vessels (Gelin, 1961) and could thus provide a possible explanation for the decreased nasal mucosal blood flow in the allergic reaction.

The decreased blood flow might partly be due to an adrenergic influence since stimulation of alpha-adrenoceptors decreases the blood flow in the human nasal mucosa (Bende, 1982 b). It has been suggested that adrenoceptors may play an important role in atopic diseases (Szentivanyi, 1968; Pelikan & de Vries, 1974; Djurup, 1981; Hegardt, 1981).

The marked oedema in the nasal mucosa, due to the increased vascular permeability, might cause a stasis of the venous out-flow and thereby a reduced blood flow. The present finding that the injection of ^{133}Xe in the swollen allergic mucosa caused a slight bleeding, which is rarely seen in normal mucosa, might indicate an increased venous pressure due to venous stasis.

It is not possible from the present investigation to evaluate the importance of these proposed mechanisms but all three might to some extent be responsible for the decreased blood flow in the allergic reaction.

The allergen provocation in this study was not performed with an exactly known amount of pollen in a graded and strictly standardized way. The amount of pollen given could thus be larger than that inducing an ordinary attack of allergic rhinitis in the allergic subjects. Our intention was, however, in this preliminary study, just to provoke a clinically obvious allergic reaction, and to find out if the blood flow in the nasal mucosa was changed in any direction. Nor was a placebo provocation made to eliminate the possibility of an unspecific reaction in the nasal mucosa. It seems unlikely, however, that the nasal reaction, induced by pollen provocation, should be a mere unspecific reaction since it was of an unquestionable allergic type clinically and elicited by pollen known to give the subjects' allergic symptoms and a positive skin reaction.

The findings in this work should encourage further detailed studies of the complex action of the different mediators on the vascular bed of the nasal mucosa.

TABLE I. Blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$) in the nasal mucosa before and after provocation with pollen allergen in 10 subjects with allergic rhinitis.

Age (years)	Sex	Allergen (pollen)	Blood flow	
			Before	After provocation
18	f	timothy	29	22
19	f	timothy	47	44
19	f	rye	39	22
23	f	birch	54	26
25	f	birch	48	26
26	f	ryegrass	43	22
28	m	birch	27	12
30	f	timothy	41	29
31	m	meadow fescue	45	16
41	m	timothy	44	39
mean 26		mean $\pm$ SEM	42 $\pm$ 2	26 $\pm$ 3

TABLE II. Blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$) in the nasal mucosa before and after histamine in allergic and non-allergic subjects.

	Age	Sex	Blood flow	
			Before	After histamine
Allergics	16	m	27	68
	17	f	47	63
	20	m	42	42
	20	m	40	56
	24	f	40	63
	26	f	40	54
	26	f	43	52
	28	m	27	61
	29	f	39	57
	43	m	44	59
			39 $\pm$ 2	58 $\pm$ 2 (mean $\pm$ SEM)
Non-allergics	24	f	24	53
	26	f	50	67
	31	m	36	53
	33	m	45	62
	34	f	29	60
	35	f	30	59
	37	m	35	69
	40	f	36	58
	55	f	27	41
	62	f	31	53
			34 $\pm$ 2	58 $\pm$ 2 (mean $\pm$ SEM)

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THE ROLE OF ADRENOCEPTORS IN THE CONTROL OF
HUMAN NASAL MUCOSAL BLOOD FLOW

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ABSTRACT

The blood flow in the human nasal mucosa is controlled by the functional state of the resistance vessels. This blood flow was studied by means of the ^{133}Xe wash-out method. Using topical application of drugs which stimulate or block adrenoceptors, including clinical doses of nasal decongestants, the adrenoceptors of the resistance vessels in the mucosa were classified. The results suggest that stimulation of α_2 -adrenoceptors cause a reduction of nasal mucosal blood flow; stimulation of α_1 and β_2 -adrenoceptors seems to have no significant effects. Drugs which selectively stimulate α_2 -adrenoceptors as well as those with preference for α_1 -adrenoceptors cause nasal decongestion. To avoid the negative effects of a nasal mucosal blood flow reduction, it is suggested that a nasal decongestant with α_1 -adrenoceptor stimulating effect should be preferable to a drug acting mainly on α_2 -adrenoceptors, provided that the decongestive effects are equal.

INTRODUCTION

Nasal mucosal blood vessels are surrounded by adrenergic nerves. This has been shown both for the capacitance vessels regulating mucosal blood content, and for the resistance vessels controlling mucosal blood flow.^{1,2} Most vascular beds contain both contraction-mediating α -adrenoceptors and relaxation-mediating β -adrenoceptors.³ In the nasal mucosal vessels, there is a functional predominance of α -adrenoceptors. Stimulation of these produces a decreased blood content and decreased blood flow in the nasal mucosa of both animals⁴⁻⁶ and man.^{7,8} The existence of β -adrenoceptors in the nasal mucosal vessels has been investigated in several studies. Thus, β -adrenoceptors could not be demonstrated either in the capacitance vessels of the dog⁴ or in the exchange vessels of the cat,⁶ but have been demonstrated in both resistance⁹ and capacitance¹⁰ vessels of the cat. Also in man the presence of β -adrenoceptors in the nasal mucosal vessels is uncertain. Grobler¹¹ reported that the β -adrenoceptor agonist isoproterenol increased nasal airway resistance, indicating dilatory action on the capacitance vessels, while Cohen¹² could not verify such an effect. Also McLean et al¹³ reported increased nasal airway resistance after intranasal application of isoproterenol, and this effect could be blocked by propranolol, a β -adrenoceptor antagonist, supporting the assumption that β -adrenoceptors were involved in the capacitance function. Recently, the selective β_2 -adrenoceptor agonist, fenoterol, was shown to produce a slight but significant increase of the nasal airway resistance^{14,15} in a double-blind comparison with placebo. However, other β_2 -adrenoceptor agonists, terbutaline and KWD 2131, were not found to influence nasal airway resistance significantly.¹⁶

These contradictory results make further investigations

desirable. As previous studies in man have been performed with rhinomanometric techniques, which mainly reflect the capacitance function, it should be of interest to also study the existence of adrenoceptors in the resistance vessels. This can be done by means of the ^{133}Xe wash-out method.¹⁷ In the present investigations this method was used to study the effects of α and β -adrenoceptor agonists on human nasal mucosal blood flow, and an attempt was made to identify the adrenoceptors of importance in the function of the resistance vessels.

MATERIAL AND METHODS

The investigations were performed on 43 healthy subjects, 9 men and 34 women, aged 19-67 years, with normal rhinoscopic findings. They were without history of nasal allergy or frequent common colds. Some subjects participated in more than one investigation.

Blood flow measurement

The blood flow in the nasal mucosa was studied by means of the ^{133}Xe wash-out method.¹⁷ Thus, 0.1 ml ^{133}Xe in a saline solution containing 1-10 MBq was injected into the mucosa of the inferior turbinate. The elimination of the isotope was followed with a scintillation detector. The blood flow was calculated from the initial slope of the first 5 min of the wash-out curve.

Drugs

The following drugs were used: 1. Phenylephrine hydrochloride (α_1 -adrenoceptor agonist) 2.5 mg/ml.* 2. Oxymetazoline chloride (α_2 -adrenoceptor agonist) 0.1 or 0.5 mg/ml.** 3. Clonidine hydrochloride (α_2 -adrenoceptor agonist) 150 $\mu\text{g}/\text{ml}$ *** 4. Yohimbine chloride (α_2 -adrenoceptor antagonist) 0.5 mg/ml.**** 5. Terbutaline sulphate (β_2 -adrenoceptor agonist) 25 mg/ml.***** The substances were applied to the surface of the inferior turbinate 15 min before recording commenced. The used dosages of the nasal decongestants, phenylephrine and oxymetazoline, were those normally used in the clinic.¹⁸ The dosages of the other substances were chosen after pilot experiments showing effects on the vascular bed, or in the case of terbutaline, after systemic side effects were observed.

* Neosynephrine[®], Winthrop, GB

** Nezeril[®], Draco, Sweden

*** Catapresan[®], Boehringer Ingelheim, FRG

**** Merck, FRG

***** Draco, Sweden

Procedure

I. The effect on nasal mucosal blood flow after topical application of 0.1 ml (0.25 mg) phenylephrine and 0.1 ml (0.05 mg) oxymetazoline was compared in 6 subjects (3 men and 3 women, aged 19-31 years, mean 25 years). The investigations with the two drugs were performed on different days.

II. The corresponding action of 0.35 ml (~50 µg) clonidine was investigated in 5 subjects (1 man and 4 women, aged 21-52 years, mean 31 years) and compared to the "normal" blood flow, ie blood flow before drug administration.

III. The effect of 0.4 ml (0.2 mg) yohimbine was studied in 4 women (aged 24-35 years, mean 31 years) and compared with their "normal" blood flow.

IV. The effect of 0.1 ml (0.01 mg) oxymetazoline was compared with the effect of 0.4 ml (0.2 mg) yohimbine and an immediately following application of 0.1 ml (0.01 mg) oxymetazoline in 5 women (aged 20-48 years, mean 28 years).

V. The effect of 0.4 ml (0.2 mg) yohimbine directly followed by application of 0.35 ml (~50 µg) clonidine was studied in two of the subjects in group III.

VI. The effect of 0.1 ml (2.5 mg) terbutaline on blood flow was compared with the "normal" blood flow in 13 subjects (1 man and 12 women, aged 20-67 years, mean 37 years).

VII. The effect of 0.1 ml (0.05 mg) oxymetazoline was compared with the effect of the same dose oxymetazoline and 0.1 ml (2.5 mg) terbutaline in 13 subjects (4 men and 9 women, aged 19-39 years, mean 31 years). These determinations were performed on different days, to

exclude influence of the first determination on the second.

Statistics

Statistical analyses were performed using the paired t test. p -values less than 0.05 were considered significant.

RESULTS

All values of blood flow are expressed as mean $\pm$ SEM in $\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$.

I. Oxymetazoline (0.05 mg) caused a marked decrease of blood flow in the human nasal mucosa, from 38.4 ± 2.9 to 21.5 ± 2.8 . The difference is statistically significant ($p < 0.01$). After phenylephrine (0.25 mg), the blood flow of the same subjects was 33.7 ± 3.1 . Compared to the "normal" blood flow, this difference is not statistically significant (see Table 1).

II. Clonidine ($\sim 50 \mu\text{g}$) decreased the blood flow significantly ($p < 0.01$), from 42.8 ± 2.8 under "normal" conditions to 26.4 ± 5.1 after clonidine administration (Table 2).

III. Yohimbine (0.2 mg) did not change the "normal" mucosal blood flow significantly. "Normal" blood flow was recorded as 39.6 ± 3.9 , and after yohimbine the mean blood flow was 40.8 ± 4.1 (Table 3).

IV. Oxymetazoline (0.01 mg) caused a significant decrease ($p < 0.01$) of blood flow, from 38.3 ± 1.8 under "normal" conditions to 22.6 ± 2.1 (Table 4). The application of yohimbine (0.02 mg) just before oxymetazoline (0.01 mg) decreased the blood-flow-reducing effect of oxymetazoline to 34.5 ± 3.5 . Compared to "normal" blood flow, this reduction is not statistically significant (Table 4).

V. In the two cases, in which the effect of yohimbine (0.2 mg) on clonidine-induced reduction of blood flow was investigated, a slight inhibitory effect was found (Table 2).

VI. The effect of terbutaline (2.5 mg) on "normal" blood flow was not statistically significant. The

blood flow decreased from 41.1 ± 3.1 to 36.4 ± 2.6 (Table 5).

VII. The decreased blood flow after topical administration of 0.05 mg oxymetazoline (21.6 ± 2.6) was not significantly influenced by 2.5 mg terbutaline (23.6 ± 2.9) (see Table 6).

Of 26 subjects who received terbutaline, a mild tremor was noted in 8. Otherwise, no side effects were observed in or reported by the subjects.

Table 1. Nasal mucosal blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$) in six healthy subjects under "normal" conditions, after topical administration of phenylephrine (0.25 mg) and oxymetazoline (0.05 mg).

Sex	Age (years)	"Normal"	Phenylephrine	Oxymetazoline
f	31	33.4	34.8	17.6
m	29	26.3	32.3	25.1
f	26	41.7	41.2	34.0
f	22	42.8	29.8	20.9
m	20	48.6	20.6	20.3
m	19	37.3	43.6	11.2
mean $\pm$ SEM		38.4 $\pm$ 2.9	33.7 $\pm$ 3.1	21.5 $\pm$ 2.8

Table 2. Nasal mucosal blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$) in five healthy subjects under "normal" conditions and after topical administration of clonidine ($\sim 50 \mu\text{g}$). In two subjects, the inhibitory effect of yohimbine (0.2 mg) is tested.

Sex	Age (years)	"Normal"	Clonidine	Yohimbine + Clonidine
f	52	46.0	22.8	29.9
f	35	47.6	29.0	-
m	25	48.5	47.2	-
f	24	40.0	18.4	24.1
f	21	31.7	14.6	-
mean $\pm$ SEM		42.8 $\pm$ 2.8	26.4 $\pm$ 5.1	

Table 3. Nasal mucosal blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$) in four healthy women under "normal" conditions and after topical administration of yohimbine (0.2 mg).

Age (years)	"Normal"	Yohimbine
35	47.6	43.3
35	26.9	27.6
30	42.8	42.5
24	41.0	49.9
mean $\pm$ SEM	39.6 $\pm$ 3.9	40.8 $\pm$ 4.1

Table 4. Nasal mucosal blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$) in five healthy women under "normal" conditions and after topical administration of oxymetazoline (0.01 mg) without and with inhibition with yohimbine (0.2 mg).

Age (years)	"Normal"	Oxymetazoline	Yohimbine + Oxymetazoline
48	44.3	23.6	22.9
28	37.0	28.8	46.1
24	40.0	20.6	29.2
21	31.7	25.4	38.4
20	38.6	14.6	35.7
mean $\pm$ SEM	38.3 $\pm$ 1.8	22.6 $\pm$ 2.1	34.5 $\pm$ 3.5

Table 5. Blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$) in 13 healthy subjects before and after topical administration of terbutaline (2.5 mg).

Sex	Age (years)	"Normal"	Terbutaline
f	20	31.7	39.5
f	24	40.0	19.4
f	24	32.6	47.4
f	26	52.4	43.2
f	31	64.3	55.3
f	34	38.9	38.5
f	35	35.5	36.4
f	35	26.9	38.7
f	35	59.5	31.2
f	42	33.7	32.8
f	52	46.0	41.4
f	56	30.7	24.7
m	67	41.3	25.0
mean $\pm$ SEM		41.0 $\pm$ 3.1	36.4 $\pm$ 2.6

Table 6. Blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot (100 \text{ g})^{-1}$) in 13 healthy subjects after topical administration of oxymetazoline (0.05 mg)(I) and oxymetazoline (0.05 mg) and terbutaline (2.5 mg)(II).

Sex	Age (years)	I	II
f	19	16.4	6.0
f	24	37.2	35.0
f	24	19.7	28.7
f	27	22.3	9.5
f	29	11.4	12.8
f	30	18.9	23.3
f	30	8.6	23.9
m	32	39.8	44.4
f	35	13.3	24.8
m	36	33.3	25.5
f	36	17.1	19.4
m	37	18.4	34.8
m	38	24.8	18.9
mean $\pm$ SEM		21.6 $\pm$ 2.6	23.6 $\pm$ 2.9

DISCUSSION

Topically applied nasal decongestants have a rapid onset of action with therapeutically used dosages. The clinical effect is obtained 3 to 5 min after application.¹⁸ The decongestant action, ie an effect mainly on the capacitance vessels, is similar for phenylephrine and oxymetazoline¹⁹, although the duration of action may be different. Both drugs are α -adrenoceptor agonists, but phenylephrine preferentially acts on α_1 and oxymetazoline on α_2 -adrenoceptors.²⁰ The present study showed that oxymetazoline and another selective α_2 -adrenoceptor agonist,²⁰ clonidine, strongly decreased the blood flow in the nasal mucosa. The topical decongestant phenylephrine did not change the blood flow significantly, although used in a therapeutically effective dosage on the capacitance vessels. These findings suggest that α_2 -adrenoceptors are of importance for the regulation of the resistance vessels. Yohimbine, considered to be a selective α_2 -adrenoceptor antagonist,²⁰ did not *per se* increase the blood flow in the nasal mucosa. The absence of action might be explained by a low α_2 -receptor mediated tone of the resistance vessels under resting conditions. The inhibitory effect of yohimbine on the oxymetazoline- and clonidine-induced reductions of blood flow, however, gives further support to the view that clinically and functionally important α_2 -adrenoceptors exist in the resistance vessels of human nasal mucosa.

It may be questioned whether the difference on nasal blood flow between two most commonly used nasal decongestants, oxymetazoline and phenylephrine, have any clinical relevance. In the present study, the important decongestive effect was not investigated. Possible differences between the drugs regarding this parameter will be decisive for the choice of therapy. However, several investigators have stressed the possible

negative effects of a blood flow reduction in the mucosa in treatment using nasal decongestants, especially in an acute rhinitis.²¹⁻²³ Therefore, a nasal decongestant with a selective α_1 -adrenoceptor stimulating effect seems preferable to a drug mainly acting on α_2 -adrenoceptors, if the decongestive effects of the substances are equal.

Hyposensitivity of β -adrenoceptors or a functional imbalance between β and α -adrenoceptors has been supposed to be a basal defect in asthma, allergic rhinitis, and other atopic diseases.²⁴ The role of the adrenoceptors in atopic diseases has been investigated in several studies, but the results are contradictory. In asthma therapy, the clinical value and efficacy of β -receptor agonists are generally accepted. The importance of β -adrenoceptors in allergic rhinitis is not definitely settled.²⁵ Demonstration and characterization of the β -adrenoceptors in the nasal mucosa may therefore contribute to an improved treatment of allergic rhinitis.

In the present study, topical application of terbutaline, a selective β_2 -adrenoceptor agonist,²⁶ neither influenced the normal nasal mucosal blood flow nor the decreased blood flow obtained after topical administration of the α -adrenoceptor agonist oxymetazoline. The used dosage of terbutaline, 2.5 mg, seems to be sufficient to induce local nasal effects since 31% of the subjects (8/26) reacted with tremor. Tremor is claimed to be a good evidence of adequate penetration of the drug through the nasal mucosa. Svensson et al¹⁶ registered tremor as well as tachycardia after nasal application of 1 mg terbutaline in some and after 10 mg in all patients. Thus, the absence of nasal effects of terbutaline in this study cannot be attributed to an insufficient dose of the drug.

The ^{133}Xe wash-out method applied to the human nasal mucosa well reflects changes of the resistance vessels without influence on the capacitance vessels.¹⁷ The sensitivity of the method has been tested^{8, 27} and, when studying the mean of a population, even small differences are detected. Thus, it is not likely that negative results depend on the sensitivity of the method. The present results therefore suggest that the human nasal mucosal blood flow is controlled mainly via α_2 -adrenoceptors, and that α_1 and β_2 -adrenoceptors are of minor functional importance.

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